REVIEW

Plasmonic gold nanoagents for cancer imaging and therapy

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Abstract
Gold nanoparticles (AuNPs) are a popular material in the field of nanoscience because of their excellent biocompatibility and unique physical and chemical properties, and have been widely used in the biomedical field. AuNPs have a simple preparation method, controllable shape and size, high electron density and atomic number, superparamagnetic properties, and radiation sensitization effect, and their optical absorbance can be adjusted to the required biological window; thus, AuNPs are suitable for cancer imaging (photoacoustic imaging, computed tomography, and magnetic resonance imaging), photothermal therapy, and radiotherapy. AuNPs can also be used as carriers to load photosensitizers or chemotherapeutic agents, and therefore, can also be used in photodynamic therapy and chemotherapy. In summary, AuNPs and their assemblies can simultaneously realize cancer diagnosis and treatment, providing a new idea in the development of precision medical treatment.

KEYWORDS
Gold nanoparticles, imaging, self-assembly, theranostics, therapy

1  |  INTRODUCTION

Treatment of cancer, a leading cause of death in humans with a very high incidence and mortality rate, has been an urgent problem. At present, chemotherapy, radiotherapy, and surgery are the main methods commonly used in cancer treatment. However, these methods have their own limitations in clinical use, making their effect in cancer treatment not ideal. Nanomaterials hold unique physical and chemical properties.\(^1\) For example, when the size of gold (Au) decreases to nanoscale (1-100 nm), Au shows distinct properties, particularly optical and biological properties, compared with bulk Au. These unique properties enable nanomaterials to be used as sensing probes, contrast agents, therapeutic agents, and drug delivery systems that provide a new modality to solve the current clinical tumor treatment problems.\(^2-6\) Nanomaterials are widely used in fundamental research concerning cancer diagnosis and therapy to make nanotechnology feasible for clinical application. It is highly meaningful to integrate different imaging and treatment methods into one system and construct a multifunctional nanostructure system for imaging, drug delivery, and therapy.

Au nanoparticles (NPs) are a representative of nanomaterials that have sufficiently developed in the biomedical field, especially in cancer imaging and therapy.\(^7-10\) AuNPs possess high biocompatibility, size controllability, nontoxicity, and excellent physiochemical properties because of their easy preparation and surface functionalization. AuNPs have tunable and superior optical
absorption because of their localized surface plasmon resonance (LSPR) effect, high photothermal (PT) conversion effect, and high extinction coefficient. Thus, AuNPs are an excellent photoacoustic (PA) imaging contrast agent and PT agent. In addition, AuNPs have a high electron density and atomic number, which improves the description of soft tissue structures with identical or similar contrast characteristic; thus, AuNPs are excellent computed tomography (CT) imaging contrast agents.[11–15] Meanwhile, AuNPs are also an excellent magnetic resonance imaging (MRI) contrast agent because of their superparamagnetic properties. Furthermore, AuNPs can also load photosensitizers or chemotherapeutic drugs for chemotherapy, radiotherapy, photothermal therapy (PTT), photodynamic therapy (PDT), and combination therapy by laser or X-ray irradiation.

Based on recent research and exploration, AuNPs have gradually developed into an integrated multifunctional diagnosis and treatment platform, such as imaging and therapy. In this review, we focused specifically on biomedical applications of AuNPs, and first summarized the applications of AuNPs in the imaging field for cancer diagnosis, including first near-infrared (NIR-I, 650–1000 nm) window PA imaging, second near-infrared (NIR-II, 1000–1350 nm) window PA imaging, ratiometric PA imaging, CT imaging, and MRI. We also discussed the use of AuNPs in cancer therapy, including PTT, PDT, X-ray therapy, chemotherapy, and combination therapy (Scheme 1).

2  CANCER IMAGING

2.1  PA imaging

PA imaging is a nondestructive biophoton imaging method based on the differences of optical absorption within biological tissues using ultrasound (US) as the medium. PA imaging combines the advantages of the high-contrast characteristics of pure optical imaging and high-penetration depth properties of pure ultrasonic imaging; an ultrasonic detector is used in PA imaging to detect PA waves instead of photon detection, and the influence of optical scattering is avoided in principle. PA imaging can provide high-contrast and high-resolution tissue images; it provides an important means to study the physiological characteristics, structural morphology, metabolic function, and pathological features of biological tissues.[16–19] It has a wide application prospect in biomedical clinical diagnosis and body tissue structure and functional imaging. PA imaging can be divided into first near-infrared (NIR-I, 650–1000 nm) and second near-infrared (NIR-II, 1000–1350 nm) window PA imaging and ratiometric PA imaging.

2.1.1  NIR-I PA imaging

NIR-I PA imaging first became the focus of PA imaging research because most of the absorption wavelengths of contrast agents were concentrated in the NIR-I window. For example, Lu et al.[20] designed mesoscopic hollow gold nanospheres (AuSPs) functionalized with poly(ethylene glycol) (PEG) having a diameter of approximately 45 nm and an optical absorption peak at 800 nm. The AuSP contrast agents exhibited the brain vasculature with greater detailed structural characteristics and significantly enhanced PA contrast, compared with contrast agents without AuSPs. In addition to AuSPs, various other morphologies of gold contrast agents, such as gold nanorods (AuNRs),[21–25] gold nanoprisms (AuNPrs),[24,25] gold nanocages (AuNCs),[26–28] gold nanostars (AuNSts),[29–31] gold-based nanoplates,[32,33] and gold-nanocrystal assembly,[34–37] have also been used in NIR-I PA imaging. PA imaging technology based on these gold-based contrast agents can realize deep tissue optical imaging with outstanding spatial resolution. However, inherent optical absorption of biomolecules, such as hemoglobin and melanin, appear to form the tissue background signals during in vivo PA imaging, thus interfering with the signals emitted by the contrast agents and affecting imaging sensitivity. To this end, Liu et al.[38] developed a US-responsive PA imaging contrast agent that AuNPs inlaid within the lipid shell of microbubbles.
(defined as Au@lip MBs) for “background-free” in vivo PA imaging. Au@lip MBs produce lower PA signals under NIR light excitation, whereas when exposed to US pulses, Au@lip MBs burst to form aggregates of Au@lip NPs, showing remarkably enhanced NIR PA signals caused by their red-shifted surface plasmon resonance effects. Therefore, by subtracting the PA signal captured before US excitation from that captured after US excitation, the tissue background PA signal can be eliminated, thus achieving highly sensitive background-free PA imaging (Figure 1A). The capability of Au@lip MBs to achieve in vivo background-free PA imaging was evaluated via intratumoral (i.t.; Figure 1B) and intravenous (i.v.; Figure 1D) injections of CuS and Au@lip MBs into CT26 tumor-bearing mice. Both i.t. or i.v. injections exhibited that Au@lip MBs were an excellent smart PA probe to enable in vivo background-free PA imaging (Figure 1C, E).

2.1.2  |  NIR-II PA imaging

The tissue penetration depth and signal-to-noise ratio of NIR-I PA imaging are unsatisfactory because of the strong absorption and scattering of biological tissues, such as lipids, skin, melanin, deoxyhemoglobin, and oxyhemoglobin, in the NIR-I window. However, the major components of biological tissue show a decreasing trend in optical absorption in the NIR-II window. Therefore, the background signals are significantly reduced and spatial resolution, signal-to-noise ratio, and tissue penetration depth are significantly improved within NIR-II window compared with those in the NIR-I window. AuNRs with a high aspect ratio can be used as excellent NIR-II PA contrast agents given the presence of tunable LSPR, excellent biocompatibility, and PT stability. For example, Emelianov et al. developed miniaturized AuNRs, which are 5- to 11-fold smaller than the regular-sized AuNRs with a similar aspect ratio, with absorbance wavelengths in the NIR-II window. Under NIR-II laser irradiation, small AuNRs have approximately three-fold higher thermal stability and 3.5-fold higher PA signal than their absorption-matched larger AuNRs. The optical absorbance of AuNR vesicles (AuNR Ves) via self-assembly method of amphiphilic AuNRs can be red-shifted by 1350 nm because of the LSPR effect; they can thus serve as longer wavelength laser irradiated NIR-II PA contrast agents. Song et al. designed an AuNR Ves nanoprobe with a light-responsive polymeric Ru-complex (PolyRu) and NIR-II IR 1061 dye for stimuli-responsive dual NIR-II fluorescence (FL) imaging and NIR-II PA imaging; this AuNR Ves can release the polymeric Ru-complex and photosensitizer IR 1061 dye sequentially on charge stimulation with NIR laser, resulting in corresponding signal changes in NIR-II PA imaging and FL imaging (Figure 2A-D). In addition to AuNRs, nanogapped gold nanoparticles (AuNNPs) are also used as NIR-II PA contrast agents. Song et al. prepared dual pH/GSH-responsive AuNNP vesicles loaded with the immune inhibitor BLZ-945 and carrying a polymeric poly(SN38-co-4-vinylpyridine) (defined as AuNNP@SN38/BLZ-945 Ves) for synergistic chemoimmunotherapy along with guided drug release by NIR-II PA imaging (Figure 2E, F). The optical absorbance of AuNNP vesicles red-shifted to the NIR-II window (Figure 2G) because of the strong LSPR effect between the adjacent AuNNPs; further, AuNNP vesicles exhibited stronger PA signals than AuNNPs in the NIR-II window following illumination by a 1260-nm light (Figure 2H). Furthermore, AuNNP@SN38/BLZ-945 Ves can be used as PA imaging contrast agents to monitor drug release in MCF-7 tumor-bearing mice. AuNNP@SN38/BLZ-945 Ves realized deeper tumor penetration ability compared with AuNNP Ves and were distributed in the entire tumor region as they disassembled into individual AuNNPs under an acidic tumor microenvironment (Figure 2I, J).

2.1.3  |  Ratiometric PA imaging

Ratiometric PA imaging with low interference of impacting PA signals from environmental factors provides an effective method for the relative quantification of pathological and physiological information of organisms both in vitro and in vivo. Various contrast agents, such as small molecules and polymers, have been used for ratiometric PA imaging; however, gold-based ratiometric PA imaging contrast agents are rarely reported. Recently, Nie et al. reported a wideband pH-responsive ratiometric contrast agent based on Au triangular nanosheets functionalized with polyaniline (PANI) using PA imaging as a diagnostic means to quantitatively detect gastrointestinal functional parameters, such as peristaltic amplitude and frequency and pH values (Figure 3A, B). When the pH changed from alkaline into acidic, PANI was reversibly protonated with a descendent optical absorption at approximately 790 nm and an unchanged optical absorption at 1200 nm (Figure 3C). PA imaging at different pH levels and PA790/PA1200 signal ratios (Figure 3D, E) demonstrated that ratiometric contrast agents can serve as a smart probe for sensing gastrointestinal pH. The pH-responsive ratiometric PA imaging strategy can be applied for quantitatively sensing duodenal and gastric pH levels in vivo. On observing, the PA790/PA1200 ratiometric signals in both duodenal and gastric ulcers were stronger than those in healthy tissue (Figure 3F-I).
2.2 | CT imaging

CT imaging is an advanced radiological technique used in the biomedical diagnostic field. CT possessed the merits of high temporal and spatial resolution, and is a simple, efficient, and convenient diagnostic tool applied in hospitals. CT has achieved excellent visualization of bone structures because of the inherent contrast between the surrounding soft tissues and electron-dense bones. Thus, CT is a good candidate method for the imaging of tumor cells. However, CT is insensitive in distinguishing different soft tissues with similar densities and thus cannot be applied on its own for cell imaging. High-Z metal NPs used as CT contrast agents in CT imaging show various advantages, such as higher photoelectric absorption coefficient, better X-ray attenuation ability, improving the sensitivity and specificity, and so on. Wherein, gold-based nanomaterials own the greatest potential for further clinical applications benefit by the superior physical, chemical, biological properties, low cytotoxicity, and available surface functionalization. AuNPs in particular can be easily synthesized in a variety of sizes by mature methods. In addition, AuNPs with a high electron density and atomic number can be an excellent contrast agent for CT imaging to improve the description of soft tissue structures with identical or similar contrast characteristic. For example, Kim et al. developed branched AuNP-coated C. novyi-NT spores (AuNP-NT) via an electrostatic deposition approach for CT imaging-guided bacteriolytic tumor therapy (Figure 4A). In a tumor mouse model, AuNP-NTs were injected into the hypoxic center of tumors under CT guidance. The infused AuNP-NTs showed significant therapeutic efficacy. Furthermore, AuNP-NTs allowed intraprocedural CT guidance to optimize and achieve targeted intratumoral delivery in mice with visceral organ tumors (Figure 4B).

2.3 | MRI

MRI is a noninvasive and common clinical diagnostic tool at hospitals. MRI contrast agents are paramagnetic or superparamagnetic substances, which can make the imaging of the lesion site clearer and improve the sensitivity and detection limit of diagnosis. Superparamagnetic iron oxide NP is a common, widely reported MRI contrast agent; however, these can cause severe protein and DNA damage and inflammation of normal tissue because of the generated reactive oxygen species (ROS). Therefore, there is an urgent need to develop a contrast agent with low or no toxicity to meet clinical requirements. Ultrasound AuNPs without ROS-associated toxicities are a premium choice because of their ease of function and clearance in vivo. For example, Kwon et al. prepared superparamagnetic AuNP clusters (SPAuNCs) comprising ultrasmall AuNPs that are sized approximately 1.4 nm. The SPAuNCs possess excellent superparamagnetic behavior and have comparable to or better $T_2$-weighted magnetic resonance than commercial $T_2$-weighted-contrast standards (Figure 5A). In addition, the use of ultrasmall AuNPs can avoid tissue damage because of outstanding biocompatibility without in vivo long-term retention problems. This indicates that ultrasmall AuNPs have promising potential as a clinically feasible MRI contrast agent for cancer theragnosis (Figure 5B).

In the abovementioned sections, we systematically summarized the application of gold nanoagents in single-modal imaging. However, single-modal imaging strategy does not simultaneously meet the requirement of specificity, sensitivity, high resolution and penetration depth, targeting, and so on. Multimodal imaging strategy can avoid the drawbacks of single-modal imaging, realizes complementary advantages. For example, Lin et al. developed a US and glutathione (GSH) dual responsive Au-MnO JNP vesicle for dual-modal NIR-II PA and MR imaging-guided synergistic sonodynamic therapy (SDT)/chemodynamic therapy (CDT) for deep orthotopic liver cancer. After intravenous administration, the enrichment of JNP vesicle in tumors can be monitored by NIR-II PA imaging. Once inside the tumor, in the presence of GSH and US stimulation, the Au-MnO JNP vesicles were first dissociated into small Au-MnO NPs for improving penetration capability, subsequently further disassembled into AuNPs as cavitation inducers to enhance SDT and release Mn$^{2+}$ to promote $T_1$-MRI and CDT efficacy.
3 | CANCER THERAPY

3.1 | PTT

PTT, a promising and noninvasive therapeutic approach, uses nanomaterials (PT agents) with high photothermal conversion efficiency (PCE) to aid their injection into the human body. PT agents are accumulated in tumor tissues using targeted recognition techniques, and light energy is converted into heat energy to kill localized tumor cells under the irradiation of external NIR light.\(^{[43,70,71]}\) Gold-based nanomaterials are excellent PT agents because of...

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**FIGURE 2** (A) Scheme showing the fabrication of an NIR light-activatable AuNR@PEG/PolyRu Ves by self-assembly of PEG and polyprodrug Ru-complex (PolyRu) functionalized AuNR. (B) PA images of AuNR@PEG/PolyRu Ves treated with or without NIR laser irradiation. *In vivo* PA images (C) and PA amplitude (D) of tumors in mice treated with the AuNR@PEG/PolyRu Ves at different time points. (E) Schematic illustration of the fabrication of AuNNP@SN\(_{38}\) Ve loaded with BLZ-945 and stimuli-responsive NIR-I PA imaging of tumor. (F) TEM images of AuNNPs and AuNNP@SN\(_{38}\) Ve, and chemical structure of PSN\(_{38}\) VP-SH. (G) UV–vis–NIR spectra of AuNNP@SN\(_{38}\) Ve, AuNNPs, and AuNPs. (H) PA images of different concentrations of AuNNP@SN\(_{38}\) Ve and AuNNPs. PA images of tumor-bearing mice treated with AuNNP@SN\(_{38}\)/BLZ-945 Ve (I) or AuNNP Ve (J) at different time points. (A–D) Reproduced with permission.\(^{[46]}\) Copyright 2020, Ivyspring International Publisher. (E–J) Reproduced with permission.\(^{[47]}\) Copyright 2020, American Chemical Society

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**FIGURE 3** (A) Schematic illustration of the design and synthesis of ratiometric PA imaging nanoprobe. (B) Proposed mechanism of diagnosis strategy of gastric and intestinal diseases via quantitative PA imaging. (C) The absorption spectra of the nanoprobe in different pH solution, (D) PA imaging, and (E) ratiometric PA\(_{790}/\)PA\(_{1200}\) values of the nanoprobe. (F) Schematic diagram of gastric microenvironment responsive nanosensor, (G) US imaging, PA imaging at 790 and 1200 nm, and ratiometric PA imaging of stomach. (H) Schematic diagram of duodenal microenvironment responsive nanosensor. (I) US imaging, PA imaging at 790 and 1200 nm, and ratiometric PA imaging of duodenum. Reproduced with permission.\(^{[59]}\) Copyright 2019, American Chemical Society
FIGURE 4  (A) Schematic illustration of AuNPs-based probe for CT imaging-guided bacteriolytic tumor therapy. (B) In vivo CT imaging-guided bacteriolytic tumor therapy of tumor-bearing mouse model. Reproduced with permission. [61] Copyright 2017, Wiley-VCH
FIGURE 5  (A) Schematic illustration of superparamagnetic AuNPs that were synthesized on protein particle scaffolds for MRI-guided cancer theragnosis. (B) In vivo MRI in tumor-bearing mouse model. Reproduced with permission.[67] Copyright 2017, Wiley-VCH

their excellent biocompatibility and outstanding PCE and have been widely applied in PTT.[8,72–73] For example, Gao et al.[74] developed photolabile AuNPs functionalized with a diazirine terminal group of PEG. The diazirine group coated on the AuNP surface was covalently cross-linkable with 405-nm light irradiation and thus formed AuNP aggregates, resulting in a red-shifted optical absorbance peak at 808 nm and enhanced PCE, and significantly improved the efficiency of PTT for cancer (Figure 6A). The NIR-II window holds much higher maximum permissible exposure (MPE) and has better tolerance of biological tissue than the NIR-I window; it is, therefore, more suitable for cancer PTT. Duan et al.[75] designed a compact hyperbranched structure, Au plasmonic blackbodies
FIGURE 6  (A) Schematic illustration of light-responsive *in situ* Au aggregation and enhanced PTT. (B) Schematic illustration of AuPBs with closely matched NIR-I and NIR-II photothermal activities. (C) Comparative PTT of AuPBs under MPE of NIR-I and NIR-II irradiation; (D) UV−vis−NIR spectra of AuPBs at various stages of synthesis. (E) Photothermal performance of AuPBs dispersion insulated by 10 mm thick chicken breast tissue. (F) Proposed mechanism of *in vivo* PTT on tumor covered by 5 mm of chicken breast tissue after laser illumination. (G) Tumor growth curve of different treatment groups. (H) Photothermal images of tumor-bearing mice under 1064 nm laser illumination and (I) their relative tumor volume. (A) Reproduced with permission. [74] Copyright 2017, WILEY-VCH. (B–I) Reproduced with permission. [75] Copyright 2018, American Chemical Society.
\( (\text{AuPb}s), \text{with a strong optical absorption range from the} \) visible light region to the NIR-II window for NIR-I and NIR-II PTT (Figure 6B-D). \( \text{In vitro} \) and \( \text{in vivo} \) assays exhibited that the most significant merit of NIR-II PTT is a higher MPE value of NIR-II laser compared with that of NIR-I laser (Figure 6E-I), indicating that the potential clinical application value of NIR-II PTT is superior to that of NIR-I PTT.

### 3.2 PDT

PDT is a new method for the treatment of tumors with photosensitive drugs and laser activation. Irradiation of tumor sites with specific wavelengths of light can activate photosensitive drugs that selectively aggregate in tumor tissues, triggering photochemical reactions to produce high levels of \( \text{ROS} \) to destroy tumor cells. AuNPs, new-generation photosensitizers, will transfer energy to the surrounding oxygen to generate highly active singlet oxygen. This singlet oxygen can then oxidize with nearby biomolecules, producing cytotoxicity and killing tumor cells. Compared with conventional cancer therapy, PDT has the advantage of effective and accurate treatment, with minimal side effects. \( \text{Gao et al.} \)\[81\] reported a ROS-mediated therapy with Au nanoclusters and photosensitizer Chlorine 6 (Ce6) coloaded into \( \text{pH-sensitive liposomal nanocomposites. Au nanoclusters} \) can generate more intracellular ROS by suppressing thioredoxin reductase (thioredoxin systems are vital intracellular antioxidant defense systems) in cancer cells, resulting in severe mitochondrial damage and obviously improving the effect of PDT (Figure 7A). Although AuNP-photosensitizer conjugates are the most important nanoplatforms for cancer PDT, conventional photosensitizer-based PDT is induced by light illumination and depends on oxygen, thus fails to be effective in hypoxic tumors. To address this issue, Yang \text{\textit{et al.}} \[82\] developed an excellent photodynamic agent, \( \text{g-C}_3\text{N}_4 \) loaded with AuNPs, for PDT of hypoxic tumors. The integration of AuNPs into the nanoplatform significantly increased the electron/hole separation because of enhanced optical absorption efficiency at 670 nm, which leads to high level of ROS generation through a photocatalytic water-splitting reaction (Figure 7B).

### 3.3 Radiotherapy

Radiotherapy is a type of local treatment for tumors with radiations such as X-rays. The role and importance of radiotherapy in the treatment of malignant tumors is becoming increasingly prominent. \( \text{A radiosensitizer is a chemical or pharmaceutical preparation, which can} \) change the sensitivity of tumor cells to radiation when applied simultaneously with radiotherapy, thus increasing the killing effect of radiation on tumor cells. \( \text{AuNPs may be a preeminent radiosensitizer in radiotherapy because AuNPs are h-Z materials with strong X-ray attenuation capabilities, excellent biocompatibility, and facile size control; furthermore, they expedite the breakage of DNA strands when irradiated with X-rays.} \[88\] For example, Wang \text{\textit{et al.}} \[89\] developed ultrasmall AuNPs coated with tumor microenvironment-responsive multifunctional peptides (Au@Tat-R-EK NPs) that showed a sufficiently stable blood circulation property and cathepsin B-responsive surface variation, resulting in a passive cancer cell accumulation capability. Furthermore, the responsive Au@Tat-R-EK NPs exhibited excellent radiosensitizing cytotoxicity \textit{in vitro} and superior therapeutic outcomes \textit{in vivo} (Figure 8A, B). However, small AuNPs hold weak long-term tumor retention and can easily flow back into the surrounding tissues or the blood circulation, leading to severe side effects. To overcome these limitations, Liu \text{\textit{et al.}}\[90\] reported an AuNP system wherein tumor acidic microenvironment-induced aggregation of approximately 30-nm AuNPs showed efficient radiosensitization for enhanced radiotherapy. On reaching into the tumor tissues, the negative surface charge of AuNPs, in response to the acidic pH, transformed into a positive charge, leading to subsequent electrostatic attraction with negatively charged AuNPs and thus forming the large-sized AuNP aggregates, resulting in prolonged tumor retention capability by blocking the backflow of AuNPs and significantly enhancing the X-ray radiotherapy outcome (Figure 8C, D).

### 3.4 Chemotherapy

Chemotherapy uses chemotherapeutic drugs to kill cancer cells. Chemotherapy is one of the most effective ways to treat cancer, along with surgery and radiotherapy, which are the three major treatment modalities for cancer. However, conventional chemotherapy has several shortcomings, such as nonspecific distribution of chemotherapeutic drugs causing toxicity in normal tissues and the development of drug-resistance. \[91\] Therefore, the main aim of chemotherapy is to improve the enrichment of therapeutic drugs in cancer cells, thereby decreasing toxic side effects and increasing treatment efficacy. \[92,93\] To this end, the development of efficient drug delivery systems is essential. AuNP-based nanocarriers are an attractive candidate for drug delivery given their high loading capacity and low toxicity. For example, Li \text{\textit{et al.}}\[94\] developed a \( \text{pH-sensitive drug delivery vehicle that included multifunctional AuSP assemblies encapsulated by a polyacrylic} \)
FIGURE 7  (A) Schematic illustration of Au-based nanocomposites with enhanced PDT effect by inhibiting thioredoxin reductase (TrxR). (B) Schematic illustration of the hybrid g-\(C_3N_4\)-AuNP-based PDT. (A) Reproduced with permission.\(^{[81]}\) Copyright 2017, WILEY-VCH. (B) Reproduced with permission.\(^{[82]}\) Copyright 2019, American Chemical Society
acid (PAA)/CaP shell (AuNCs-A@PAA/CaP NPs) with a high doxorubicin (DOX) loading ability for dual-modal FL imaging and CT-guided cancer chemotherapy (Figure 9A). The results showed that AuNCs-A@PAA/CaP NPs not only presented outstanding FL and CT contrast imaging but also showed efficient tumor ablation, providing superior chemotherapeutic outcomes without apparent systemic damage to healthy tissues. Although a delivery system is generally used, over 50% of the chemotherapy dose still stays in healthy tissues. Thus, making normal cells or organs resistant to cytotoxicity is another way to improve chemotherapy outcomes. For example, Tang et al.\textsuperscript{[95]} developed a novel method for capturing chemotherapeutic drugs in normal cells to reduce their cytotoxicity and improve pharmacotherapy. They prepared nanocomposites of gold-oligonucleotides (Au-ODNs) that were selectively enriched in hepatocytes and removed DOX-triggered hepatotoxicity that could capture DOX within normal cell to block nuclear access, thereby improving the normal cell’s ability to defend the threatening chemotherapeutic milieu (Figure 9B).

3.5 | Combination therapy

Single treatment approaches often fail to achieve the goal of complete cure in cancer. Combination therapy is a promising strategy because it can achieve complementary advantages of various treatments. For example, Wang et al.\textsuperscript{[96]} developed an Au@Rh-ICG-CM nanosystem with
excellent biocompatibility, high tumor accumulation capacity, and superior FL and PA imaging properties, consisting of a porous Au@Rh nanocatalyst, photosensitizer indocyanine green (ICG), and targeting agents (tumor cell membrane, CM) for imaging-guided self-synergistic mild PTT/enhanced PDT. Au@Rh-ICG-CM can catalyze oxygen generation from hydrogen peroxide in cancer cells and then elevate the output of cancer-toxic singlet oxygen, combining mild PTT to enhance the effect of PDT in treating cancer (Figure 10A). Chemotherapy-PTT is a combination cancer treatment method that can kill tumors efficiently, but conventional chemotherapy-PTT uses clinical general chemotherapeutics, which are often ineffective in drug-resistant tumors. To address this issue, Zeng
et al.\cite{97} prepared AuNBPs@PDA–DOX nanoparticles with pH- and photothermal stimuli-responsive drug release via polydopamine (PDA)-functionalized gold nanobipyramids (AuNBPs@PDA), and then loaded them with DOX for PA imaging-guided synergistic PTT and chemotherapy. The results showed that AuNBPs@PDA–DOX nanoparticles achieved amplified PA signal and enhanced chemotherapy-PTT, thus indicating that it is a promising candidate for a safe and efficient visualization probes for combination cancer therapy (Figure 10B). In addition, chemo-immunotherapy\cite{47} and PTT-X-ray therapy-PDT\cite{98} have also been used for combination cancer therapy.

4 | CONCLUSIONS AND OUTLOOK

Gold nanoagents have been widely used in the biomedicine field because of their easy functionalization and unique physicochemical properties, which have brought bright prospects for pharmaceutical development and cancer diagnosis and treatment. Gold nanoagents have thus become an integral part of biomedical engineering. The development of gold nanoagents is an important milestone in modern diagnosis and treatment and has resulted in rapid and efficient outcomes. In this review, we systematically summarize the applications of gold nanoagents in biomedicine, including imaging (PA
imaging, CT, and MRI) and therapy (PTT, PDT, radiotherapy, chemotherapy, and combination therapy).

Although gold nanoagents have been widely explored in the biomedical field, there are still some issues that need our special attention. First, effective utilization rate needs to be ensured. It is a promising development goal suggesting the use of fewer AuNPs to achieve the same imaging and therapeutic effects, thereby reducing potential risks to the frail body of the patient. At present, ameliorating the biocompatibility by coating PEG, polypeptide, natural proteins, tumor microenvironment-responsive polymers and targeting molecules to gold nanoagents surface is a common approach to improve the utilization ratio. However, how to effectively use and combine these methods to synthetize products for practical clinical application remains to be further studied. Second, biodegradation and rapid renal clearance abilities of gold nanoagents need to be considered. The clearance rate of the NPs mainly depended on their composition, size, surface modifications, and targeting functionality. The smaller size of the NPs contributes to faster clearance. The sizes of NPs less than 100 nm have been considered to be effective in enhancing permeability and retention effects and renal clearance. The sizes less than 6 nm are usually cleaned by kidney no matter what charge they are, more than 10 nm are more prone to be cleaned by the liver. However, the size of 6–10 nm occurs renal elimination with a result that the elimination of the positive NPs faster than the negative or neutral NPs. Besides, functionalized natural proteins and PEG with low molecular weight can be used as an effective ligand to gold nanoagents surface for improving systematic clearance capabilities. Furthermore, pharmacological toxicity studies on gold nanoagents are usually short term yet lack systematic evaluation of long-term chronic toxicity.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

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