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HARNESSING GOLD NANOPARTICLES FOR TARGETED DRUG DELIVERY AND CANCER TREATMENT

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ABSTRACT

Gold nanoparticles (Au NPs) have emerged as promising radiosensitizers in various biomedical applications, including drug delivery and cancer therapy. Their unique properties, such as size, composition, morphology, and surface chemistry, can be precisely controlled through advanced synthesis and fabrication methods. Au NPs can act as contrast agents and dose enhancers in image-guided nanoparticle-enhanced radiotherapy using kilovoltage cone-beam computed tomography. Surface functionalization of Au NPs with various ligands, such as PEG, ssDNA, antibodies, peptides, drugs, fluorescence markers, and siRNA, enables them to perform multiple biomedical functions simultaneously at the molecular or cellular level. This review highlights various synthesis methods for Au NPs, including the colloidal method, galvanic replacement, and the Brust-Schiffrin method. The properties and applications of Au NPs in drug delivery and cancer therapy, such as plasmid DNA vector delivery, RNA delivery, and gold nanoparticle-based therapy, are explored. However, the potential toxicity and health impact of Au NPs need to be thoroughly investigated before clinical implementation. The review also discusses the challenges associated with drug administration and the role of biomaterials in improving medical technologies through increased control of immune signals. The synthesis and properties of Au NPs, including their core size, stabilizing agents, and surface modifications, are also discussed in detail.

KEYWORDS: Gold Nanoparticles; Drug Delivery; Cancer Therapy; Surface Plasmon Resonance; Tumor Targeting; Nanomedicine.

1. INTRODUCTION

Gold nanoparticles (Au NPs) are emerging as efficient radiosensitizers and contrast agents in biomedical and cancer therapy. Leveraging kilovoltage cone-beam computed tomography, Au NPs enhance radiotherapy by improving dosage delivery and imaging capabilities.[1,2] Recent advances in nanomaterial synthesis have enabled precise control over particle characteristics such as size, shape, and surface chemistry, which enhances stability and functionality.[3]

Biocompatible coatings and functional ligands can be applied to Au NPs, allowing them to serve multiple roles including drug delivery, cancer therapy, and multimodal imaging. Au NPs offer unique advantages due to their optical properties, ease of synthesis, and chemical stability, making them suitable for a range of biomedical applications. They have been utilized in gold nanoparticle-based therapies, RNA and DNA delivery, and as contrast agents in imaging.[4-6]

Despite their potential, it is crucial to thoroughly investigate their toxicity and health effects before widespread clinical use.[8] In addition to Au NPs, various other nanomaterials such as liposomes, carbon nanotubes, and quantum dots are employed in biomedical fields.[9] Au NPs, often referred to as "potable gold," are valued for their high x-ray absorption and localized surface plasmon resonance.[16,17] Their utility in drug delivery can be influenced by factors like vascular characteristics and immune response, which affect drug accumulation and effectiveness.[19] Advances in surface coating technology now allow for extensive functionalization of Au NPs, enhancing their role as therapeutic agents, molecular sensors, and delivery systems.[20] Other nanomaterials like liposomes, carbon nanotubes, polymeric micelles, graphene, and quantum dots are also frequently utilized in biomedical applications.[10] As NP-based technologies advance, human exposure to manufactured nanoparticles becomes more inevitable, making their benefits and characteristics

increasingly relevant.[11,13] NPs, with their small size, high chemical reactivity, and large surface area, continue to be a focus of research for drug delivery and other applications.[14] The historical use of Au NPs as "potable gold" underscores their long-standing significance, and ongoing advancements are likely to expand their applications further.[15,16]

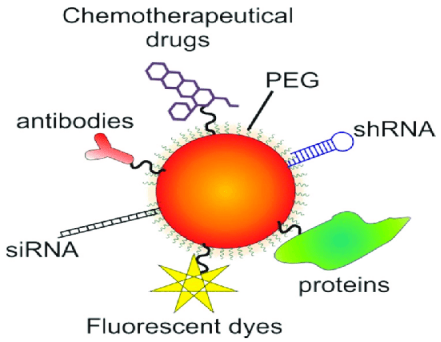

Figure 1: Representation of an Au NP for theranostics.

2. SYNTHESIS AND PROPERTIES

Gold nanoparticles (Au NPs) are commonly synthesized using the colloidal approach, which allows precise control over size, shape, and optical properties by combining a reducing agent, a metal precursor, and a stabilizing agent.[21,22]

This method produces various nanostructures, including spheres, nanorods, and nanocages.[23] Recent developments have introduced hollow Au NPs via galvanic replacement.[24] and a one-pot method by Brust and Schiffrin for creating monolayer-protected Au NPs using tetrachloroaurate and sodium borohydride or citrate.[25] The core size, ranging from 1.5 to 6 nm, is influenced by the ligand used, with larger sizes achievable through citrate reduction or ripening processes.[26] The place exchange reaction is another technique for modifying ligand compositions on Au NPs.[27] In medicinal applications, the bottom-up approach is favored, often using sodium citrate or sodium borohydride for reduction, and stabilizing agents like polyethyleneimine (PEI) are employed to prevent agglomeration.[21,27] PEI facilitates nucleic acid delivery due to its amine groups.[29] PEGylation, using polyethylene glycol (PEG), reduces the early removal of NPs from the bloodstream.[31] while biomimetic modifications and conditional PEG removal offer alternative surface modification techniques.[32,33]

Different synthetic methods for Au and other metallic NPs include sol-gel micro reactors, acidic reduction, γ-irradiation, and biosynthesis.[21] Adjusting reducing agents or chloride ions in citrate reduction can vary Au NP sizes between 19 and 47 nm.[34] Acidic stabilization and polymeric NPs, such as glutathione-capped Au NPs, enable further size control.[35,36] Seed-mediated synthesis uses halides for surface passivation and growth regulation.[37] and silver ions can alter particle morphologies.[38] Gold silica nanoshells, made by seed-mediated development, are used in imaging and targeted therapy, while gold nanorods offer adjustable near-infrared absorption with high coefficients.[39,40] Gold nanocages and hollow Au NPs are advantageous for photothermal applications due to their unique structures.[41] Emerging technologies in Au NP synthesis, including stimuli-responsive designs, are enhancing their applications in cancer therapy and drug delivery.[42]

Type of NPs	Synthetic Method	NP Size (nm)
Au	Sol-gel micro reactors	5–50
Au, Ag, Pd, Pt	PVD into liquid substrate	2–10
Pd, Pt	Reduction in acidic environment	3–40
Au	Reduction process	2–40
Au, Cu	γ-Irradiation	3–30
Cu	pH control of Cu complexes	48–150
Au, Ag, Pd	Biosynthesis	9–25
Ag	Wet chemistry	20–60

3. CELLULAR UPTAKE OF GOLD NANOPARTICLE AND CYTOTOXICITY

Nanoparticles, with sizes comparable to biomolecules, can be tailored for specific biological interactions. Gold nanoparticles (Au NPs) modified with simian virus 40 (SV40) nuclear localization signals are used for targeted nuclear delivery.[43] Techniques such as using Tat peptides or mycobacterium-coated Au NPs enable entry into the cell nucleus and cytoplasm, respectively.[44]

Surface functionalization is crucial for cellular uptake, influenced by ligand density and molecular weight, while Au NP size has minimal effect on uptake.[45] Shape also affects cellular absorption, with triangular Au NPs being

more effective in RAW264.7 cells than rod-shaped or star-shaped NPs.[46] Studies comparing hollow Au nano-cages, nanorods, and plasmons with siRNA reveal that hollow Au nanoshells load more siRNA and have better gene silencing efficiency.[47] Genotoxicity assessments of Au NPs ranging from 5 to 50 nm show that smaller particles can induce DNA damage and clastogenic effects, especially at 5 nm.[48] Toxicity varies with size, cell type, and tissue interaction, with smaller Au NPs (1-5 nm) exhibiting higher toxicity.[50] Polyethylene glycol (PEG) coating enhances transfection efficacy and reduces toxicity.[51,52] PEG-coated Au NPs show prolonged blood circulation and targeted delivery to the liver and spleen.[54]

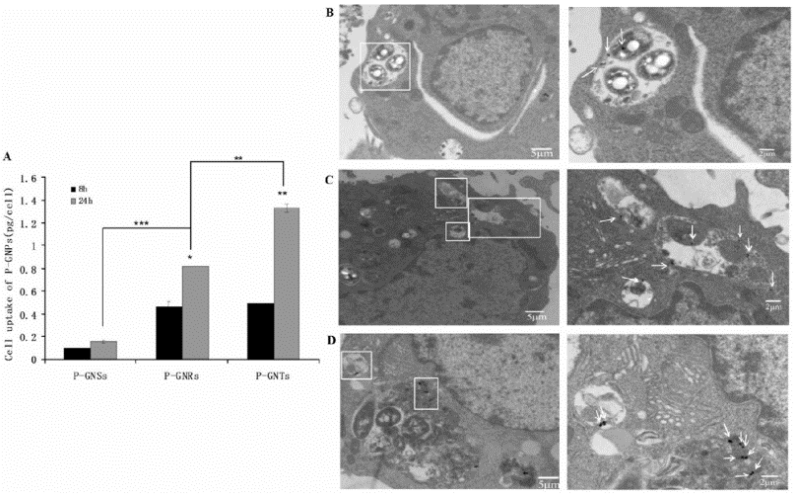

Figure 2: Cellular uptake of P-GNPs (A) and transmission electron microscopy images of RAW 264.7 after 24 h of incubation with P-GNSs (B), P-GNRs (C), P-GNTs (D). Data represent mean ± SEM (n = 3). Statistical significance is represented by * p < 0.05, ** p < 0.01, *** p < 0.001.[46] Reproduced from reference.[46] with Springer Nature under the Creative Commons Attribution 4.0 International License.

Gold nanoparticles are also utilized to overcome multidrug resistance (MDR) in cancer therapy. Au NPs quench fluorescence efficiently, making them suitable for fluorescent nanoprobe applications. For instance, doxorubicin tethered to Au NPs via PEG improves drug delivery and efficacy against P-gp mediated drug resistance.[55] Targeted delivery of siRNA using unimer polyion complex Au NPs and cyclic Arg-Gly-Asp ligands enhances gene silencing in cancer cells.[56] In liver cells, green Au NPs induce oxidative stress and DNA damage, with higher sensitivity observed in cancer cells.[57] Plasma treatment can reduce Au NP size and enhance their cytotoxicity against cancer cells.[58]

Overall, Au NPs exhibit stable chemistry, minimal toxicity, and significant potential for biomedical applications. Further research is needed to optimize their uptake, toxicity, and therapeutic efficacy.

4. GOLD NANOPARTICLE BASED DRUG DELIVERY

Nanomedicine, particularly with gold nanoparticles (Au NPs), shows promising clinical efficacy with enhanced therapeutic results and reduced toxicity. Although Au NP-based nano-drugs are not yet officially approved, research is actively exploring their potential, especially in cancer treatment and tumor targeting.[59] Au NPs are effective carriers for a range of drugs, including peptides, pDNAs, proteins, small siRNAs, and chemotherapeutic agents. Their surface can be modified with functional groups like carboxyl, amine, or thiol to improve drug delivery and protect the drug from enzymatic degradation.[60] Fucoidan, a bioactive polysaccharide, is used to synthesize Au NPs, enhancing biocompatibility and reducing toxicity compared to conventional methods.[61] pH-sensitive medications, such as Morin encapsulated in Au NPs, show effectiveness in targeting acidic tumor environments and enhancing tumor apoptosis in mouse models.[62] For bacterial infections, Au NPs improve drug delivery and effectiveness, especially when combined with antibiotics like gentamicin sulfate, which often suffers from poor membrane permeability and high solubility.[64] Innovative delivery systems use Au NPs to encapsulate multiple drug molecules, allowing effective penetration into cells.[65] Additionally, Au NPs combined with everolimus have shown promise in treating conditions like Bronchiolitis obliterans syndrome.[66] Cyclic peptide-capped Au NPs offer enhanced drug delivery due to their ability to penetrate cell membranes and deliver therapeutic agents more efficiently.[67] Recent advancements also include Au NP-based systems for fluorescence imaging and targeted drug delivery. For instance, Au NPs combined with platinum drugs and aminoanthraquinone demonstrate effective DNA binding and imaging capabilities.[69] Au NPs are being explored for intraocular drug delivery, showing potential in treating retinal conditions.[70] Moreover, cell membrane-coated Au NPs, such as those with platelet membranes, offer targeted cancer therapy

options.[71], and doxorubicin-loaded Au NPs show promise in prostate cancer treatment.[72] Testing in leukemia cells has also demonstrated encouraging results.[73]

4. 1. Plasmid Deoxynucleic Acids Vector (pDNAs) Delivery Gold nanoparticles (Au NPs) functionalized with DNA are increasingly used in drug delivery and biosensing due to their versatility and efficiency. The DNA-Au NP conjugate has shown effectiveness as a nano-carrier for drugs and genes, overcoming challenges such as nuclease degradation and blood serum interference.[74] PEGylation of DNA strands attached to Au NPs can prevent random protein absorption and protect against DNase I degradation, thereby enhancing cellular uptake and efficiency.[75] Recent advances have focused on functionalizing Au NPs with oligonucleotides through thiol modification, enabling the creation of complex nanostructures such as tetramers, trimers, and dimers. These structures offer stability and can perform multiplexed functions in biological settings, including targeting mRNA and delivering anticancer drugs.[76] Additionally, amphiphilic coatings on Au NPs, such as pyridinium amphiphiles, improve plasmid DNA delivery by influencing NP shape and size, which affects cellular uptake and DNA compaction.[77] Nanogels containing polymeric Au NPs offer a flexible delivery system, capable of encapsulating and releasing drugs with reduced cytotoxicity. Poly(N-isopropylacrylamide)-based nanogels, for example, provide biocompatibility and temperature-responsive properties, allowing for controlled NP size changes.[78][79] Liposomes, particularly those functionalized with DOTAP lipid, are also effective in gene and drug delivery, though PEG elimination from liposomes can be crucial for their efficacy.[80] Further research has demonstrated the potential of Au NPs in gene targeting, such as blocking specific genes in cancer cells and using snake venom-derived peptides like cotamine to facilitate DNA delivery.[81][82] Au NPs functionalized with Y-type DNA have been developed for detecting telomerase and releasing anticancer agents in cancer cells, providing a novel approach for cancer treatment.[83] Additionally, NIR-sensitive nanoparticles that integrate PEG, DNA strands, and Au nanorods have been explored for thermo-chemotherapy, combining heat conversion with therapeutic DNA delivery.[84]

4. 2. Ribonucleic Acids (RNAs) Delivery
Recent advancements have highlighted the potential of gold nanoparticles (Au NPs) in RNA delivery for HIV treatment and other applications. One approach involved PEGylated Au NPs with a covalent bond to thiol-modified oligoribonucleotides via a cleavable linker, N-succinimidyl 3-(2-puridyldithio) propionate (SPDP). The Au NPs were further coated with polyethyleneimine to enhance endosomal escape and cellular uptake. Anti-CD4 cyclic targeting peptides were attached to the Au NPs to improve selectivity and uptake in target cells. Each lymphocyte took up about 45,000 RNA strands, showing potential for HIV therapy despite no antiviral activity being observed.[85] RNA interference (RNAi) for gene and cancer therapy has shown promise with functionalized Au nanorods used to deliver stable hairpin RNA. This approach effectively targets human brain cancer cells, utilizing disulfide-cross-linked cleavage for endosomal escape. The high intracellular glutathione levels enable rapid RNA release, and PEGylation ensures stability and prolonged circulation, enhancing tumor accumulation and gene silencing effectiveness in brain cells. Encouraging results were observed in tumor-bearing mice.[86] Addressing the challenge of delivering drugs across the blood-brain barrier for glioblastoma, researchers explored nose-to-brain direct transport using gold-iron oxide nanoparticles. This approach incorporates microRNA for glioblastoma therapy and temozolomide delivery. The technique showed promising results in animal models, indicating its potential for clinical application.[87] In the context of triple-negative breast cancer, multilayered NPs containing metastasis suppressor microRNA (miR780) were designed for targeted delivery to reduce lung metastases. In vivo experiments demonstrated the efficacy of this approach, suggesting it could improve clinical outcomes for this aggressive cancer type.[88] For ovarian cancer, Au NPs have been used to deliver DNA, specifically examining the antitumor effects of DOX-DNA-Au NPs across three ovarian cancer cell lines: SK-OV-3, HEY A8, and A2780. The results from the EZ-Cytox cell viability assay indicated that DOX-DNA-Au NPs exhibit significant activity and could be a viable treatment option.[89]

4.3. Small Interfering Ribonucleic Acids (siRNAs) Delivery
Small interfering RNAs (siRNAs) hold significant therapeutic promise, particularly in cancer treatment. Their efficacy is hindered by challenges such as instability and low cellular uptake. Gold nanoparticles (Au NPs) have emerged as effective vectors to address these issues. In glioblastoma therapy, Au NPs encapsulated with siRNA and modified with arginine-glycine-aspartic (RGD) peptides demonstrated effective gene silencing and high transfection efficiency in U87MG cells. This was confirmed through flow cytometry, protein expression analysis, and confocal microscopy.[91] For prostate cancer, a study utilized Au NPs coated with polyethyleneimine (PEI) and conjugated with anisamide-targeting ligands to deliver siRNA targeting the ReIA gene. This approach protected siRNA from degradation and enhanced gene silencing in PC3 prostate cancer cells, showing potential for therapeutic use.[92] In melanoma, Au NPs co-delivering anti-STAT3 siRNA and imatinib mesylate achieved a significant reduction in tumor volume and weight, highlighting a promising strategy for targeting the STAT3 pathway.[93] For breast cancer, particularly involving cancer stem cells (CSCs), Au

NPs assembled with a polymer complex and targeted with specific ligands delivered siRNA effectively, resulting in strong cellular uptake and significant gene knockdown in CSC-rich cultures. This approach shows potential for improving treatment outcomes by targeting CSCs.[94] Additionally, Au NPs coated with HIV-1 TAT peptides were developed to deliver siRNA targeting the ROR1 antigen in breast cancer. This method demonstrated high cellular uptake and efficient gene transfection with low cytotoxicity, indicating its potential for treating invasive breast cancer.[95] Overall, Au NPs offer advantages in drug delivery, including longer circulation half-life, better biocompatibility, and increased cellular uptake. Future research will focus on understanding their cytotoxicity and interactions with healthy cells.

5. GOLD NANOPARTICLE BASED THEORY

Photothermal therapy (PTT) represents a promising approach in cancer treatment, leveraging the ability of nanoparticles to convert light into heat for targeted tumor destruction. Gold nanoparticles (Au NPs) are particularly effective for PTT due to their excellent biocompatibility, ease of functionalization, small size for tumor penetration, and their efficient conversion of light, especially near-infrared (NIR) light, into heat. NIR light is advantageous because it penetrates deeper into tissues compared to other wavelengths, enhancing the effectiveness of PTT.[96][97] Au NPs have shown potential in various applications, including localized heating and controlled drug delivery. Their ability to convert NIR light into heat allows for targeted hyperthermia, directly damaging or abating tumor cells.[98] Additionally, in synergistic therapies, combining drug delivery with photothermal effects has yielded promising results in breast cancer models.[99]

Multifunctional Au NPs, such as Au nanostars, have been designed for enhanced Raman scattering (SERS) imaging and NIR-induced photothermal therapy. These nanostars cover broad NIR absorption bands and exhibit effective SERS activity and photothermal effects, making them versatile tools for cancer diagnosis and treatment.[100] Hybrid systems incorporating Au NPs with heat-sensitive delivery mechanisms have also been developed. For example, hollow Au NPs have been used to deliver bupivacaine, demonstrating the potential for NIR-light-activated drug release and PTT applications.[101] Similarly, NIR-absorbing Au-Au sulfide NPs have shown enhanced tumor penetration and efficacy in photothermal cancer therapy, resulting in significant long-term tumor-free survival.[102] In radiation therapy, Au NPs can act as dose boosters, increasing the destruction of cancer cells while minimizing damage to surrounding healthy tissue. Studies have shown that adding Au NPs to the radiation therapy can enhance dose escalation and improve treatment efficacy, with higher dose escalation factors (DER) observed in smaller tumors and with specific photon beam energies.[1]

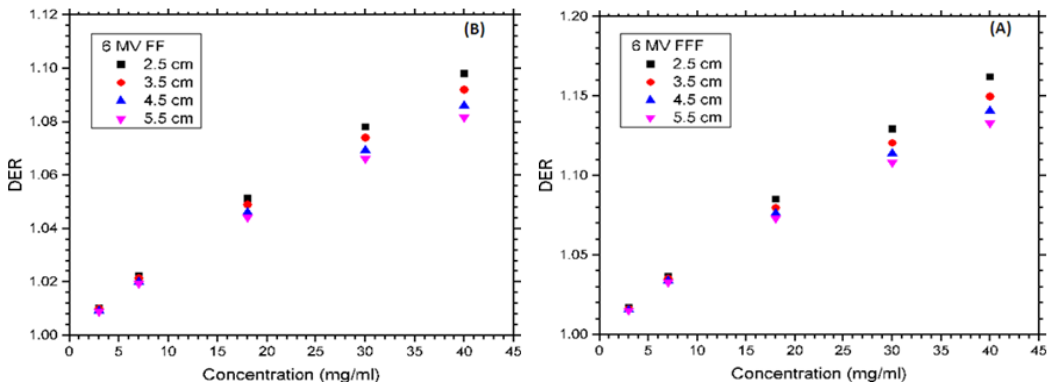

Figure 3: Relationship of the DER and Au NP concentrations, varying with different prostate sizes in the phantom using the 6 MV (A) FFF and (B) FF photon beams. Au NPs with concentrations equal to 3, 7, 18, 30, and 40 mg/mL were used. The DER was calculated as the ratio of the target dose with NP addition to the target dose without NP addition.[1] For skin cancer radiotherapy, the addition of Au NPs improves dose deposition and image contrast, with greater DER values achieved with lower photon beam energies and thinner lesions. In summary, Au NPs offer significant advantages in cancer therapy through their role in PTT, drug delivery, and radiation dose boosting. Their ability to enhance therapeutic outcomes and reduce side effects underscores the need for further research to optimize their application in clinical settings.

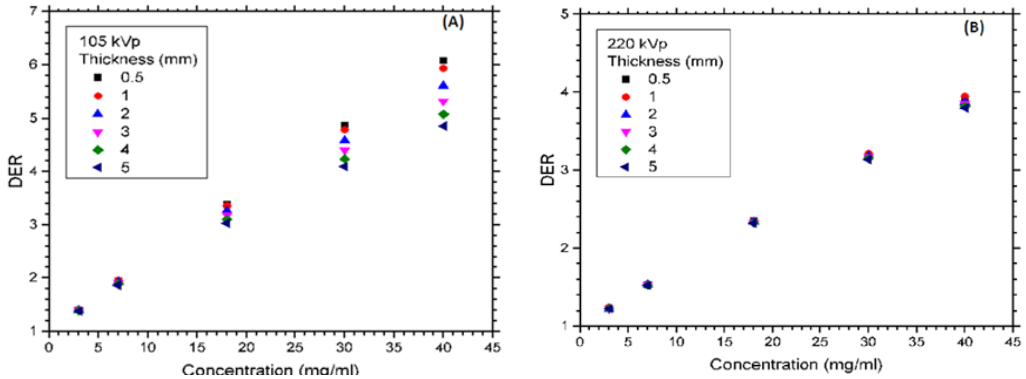

Figure 4: Relationship between the dose enhancement ratio and Au NP concentration with variation of the skin target thickness using the 105 (A) and 220 kVp (B) photon beams.[103]

6. MOLECULAR NANOPROBES

NPs interact with light and have a tuned surface plasmon resonance, which can be detected with several imaging modalities.[104] Au NPs have the ability to accumulate in tumor cells. Their abilities to produce photoacoustic signals and photothermal effects are also very valuable in medical and diagnostic imaging.[105] Au NPs have optical properties that are useful in biosensors in living cells. A surface plasmon resonance scattering image for Au NPs conjugated with anti-epidermal growth factor receptor (anti-EGFR) monoclonal antibodies in a non-malignant epithelial cell line (HaCAT) and two oral epithelial cell lines malignant (HOC 313 8 and HSC clone) has been studied. Antibody-conjugated NPs bind specifically and homogeneously to the surface of cancer cells with 600% higher affinity than non-cancer cells. This produces a sharper SPR absorption band with a red-shifted maximum compared to that of the non-cancerous cell. Diffusion images generated by these antibody-conjugated gold nanoparticles are useful for diagnosis.[106] Ultra-small gold nanoparticles less than 10 nm in diameter have shown promise in the biomedical field. Their potential applications in cancer treatment and medical imaging have not been examined. Several systems based on ultra-small gold nanoparticles are under development for use in the diagnosis and treatment of cancer. Some applications in development includes the use of ultra-small gold nanoparticles for tumor visualization and bioimaging in various fields such as magnetic resonance imaging, fluorescence imaging, photoacoustic and X-ray scattering imaging. They are also studied in tumor chemotherapy, radiotherapy and gene therapy.[107]

7. CONCLUSION

Gold nanoparticles have high potential in cancer therapy and drug delivery applications. Although gold nanoparticles are not widely used for clinical applications, research on gold nanoparticle drug delivery, gene therapy, photothermal therapy, and radiation therapy all show promising results and are shown to be potentially viable solutions in the future. Based on the promising results obtained in the present and the progress expected in the future, it is certain that gold nanoparticles will continue to play an important role in improving the biomedical field, especially in drug delivery and anticancer therapy. However, some limitations in the application of gold nanoparticles as nanocarriers or radiosensitizers, such as cytotoxicity, non-biodegradability and modulation of cellular responses, should not be overlooked and should be studied in detail.

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