



Nanogold: a versatile therapeutic agent in oncology

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Abstract

Nanogold is an emerging and versatile therapeutic agent since decades. Nanoogold and its'complexes can be synthesized through different ways. Its' use in oncology as a drug delivery vehicle, photothermal agent, Nucliec acid delivery vehicle and a photodynamic agent has been investigated by many researchers. Au nanoparticles (AuNPs) are nanovehicles with inimitable optical properties and incredible biocompatibility which have the property to effect the fate of cancer by delivering anticancer drugs, nucleic acids to cancer cells and tissues. Herein different modes of applications of nanogold in oncology and the challenges during the use of nanogold as therapeutic agent have been discussed. Nanogold and its' complexes can be used as a biocompatible and efficient tool to treat and diagnose different types of cancer which are discussed with details in this review.

Key words gold nanoparticles, photothermal therapy, drug delivery, nucliec acid delivery

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Introduction

The design, production of different materials and systems at a controlled nanosize and their applications is termed as nanotechnology [1]. It is well recognized that nanomaterials have vast applications in different areas and researchers claim that nanotechnology would bring a great revolution in industrial as well as agricultural areas [2]. Nanoparticles have great importance and researchers are interested to use them to improve drug delivery as well as in-vitro diagnostics, bioimaging therapies and active implants. The nanomaterials having size of 1-100 nm are termed as nanoparticles which are also defined by American Society for Testing and Materials (ASTM) standard [1]. Cadmium selenide quantumdots, Au nanoparticles and carbon nanotubes are the extensively studied nanomaterials [3-5]. In order to reduce the incidence and mortality of gastrointestinal cancers, as well as improve the survival rate of patients, it is critical to excogitate the treatment and diagnosis of gastrointestinal cancers. In recent years, noble metal nanoparticles have received significant attention in cancer medical research due to their unique efficacy and specificity in imaging, diagnosis, and therapy [5]. Gold nanoparticles (GNPs) are widely used, particularly in cancer research, because of their ease of synthesis, adjustable size and shape, remarkable biocompatibility, unique optical properties, and surface plasmon resonance (SPR) properties [6]. Multi-shaped Au NPs are fabricated to treat various kinds of cancer. The expression of surface receptors, and tumor environment are utilized for photothermal therapy [7], immunotherapy [8], photodynamic therapy [9], gene therapy [10], targeted therapy [11], and a combination of multiple treatments [10], allowing the integration of cancer diagnosis and treatment.

The unique optical activity of gold nanoparticles developed them ideal nanomaterials in biosensing, photothermal and imaging agents for medical diagnosis which is comparatively uncommon for the other inorganic nanomaterials. The high surface to volume ratio and large surface activity bestow the quality of funtionalization and large loading amounts. various molecules, including drugs, nucleic acids (DNA or RNA), proteins or peptides,

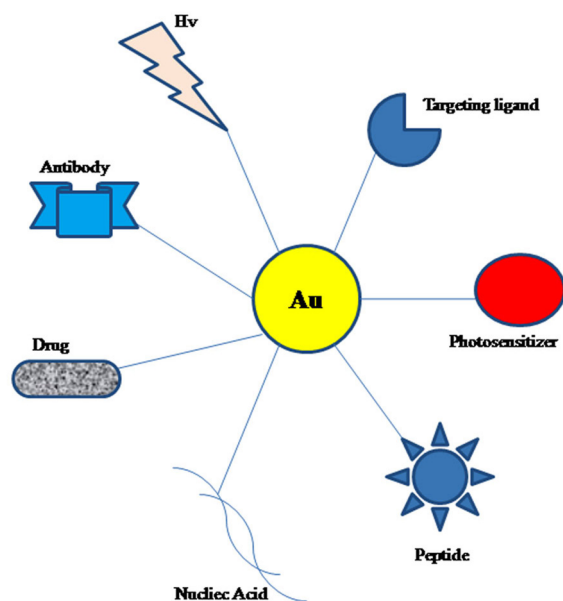


Figure 1. Different Au based nanocomplexes for efficient biological activities and diverse medical applications [25]. Hv, irradiation with light.

antibodies, targeting ligands, and other molecules can directly or indirectly conjugate and interact with AuNPs (Figure 1) [12]. The blending capacity and miscellany highly enhance their biological properties and widen the range of their potential anticancer properties. Besides, AuNPs have been found to be comparatively stable in physiological medium because of the modification of amphiphilic materials, [13] and biocompatible, nontoxic due to inert nature of metallic gold. All of these properties have rendered AuNPs ever more popular nano-vectors in oncology. This review focuses on various widely utilized AuNPs applications in cancer treatment and diagnostics, including drug and nucleic acid delivery, photodynamic therapy (PDT), photothermal therapy (PTT), and X-ray computed tomography (CT) imaging, among others.

AuNPs with different Morphologies

The light-scattering features of gold microparticles in suspension are found Michael Faraday in 1857, which is termed as the Faraday-Tyndall effect [14]. Hirsh et al. discovered after 50 years that the irradiation of AuNPs with an electromagnetic wavelength at 820 nm would increase the surrounding temperature, which could be used as a remedy of solid tumor [15]. The U.S. The Food and Drug Administration (FDA) of USA in July 2019 approved an oral medicine based on AuNPs (CNM-Au8, Clene Nanomedicine, Inc.) for the treatment of amyotrophic lateral sclerosis (ALS) [16]. Which showed that AuNPs are safe and This demonstrated that GNPs are a safe and reliable remedy with great potential for cancer treatment. The polarization of free electrons and the distribution of surface charges are determined by size [17, 18]. AuNPs are modified in different shapes which shift the scattering/absorption peak to the NIR window, permitting AuNPs in the deep tissue to receive incident light energy [13]. Differnet assays have been reported in the last 20 years that different shapes of AuNPs including nanoclusters [19], nanorods [20, 21], nanoplates [20], nanoshells [22], nanocages [23], and nanostars [24] are successfully and widely studied in various cancer diseases. Particularly, Au-nanorods, nanocages, and nanoclusters have been widely used in gastrointestinal cancer (Figure 2) [25].

AuNPs in Drug Delivery

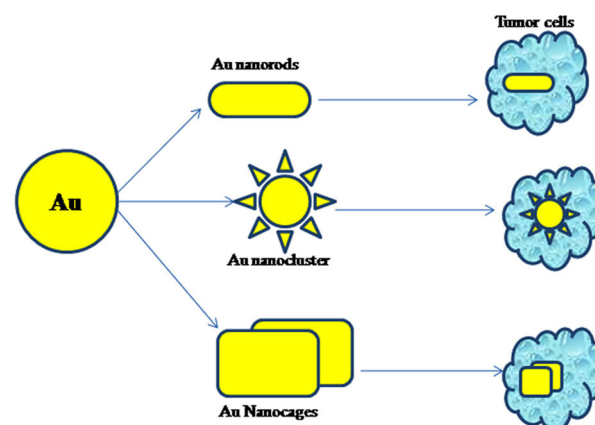


Figure 2. different morphologies of AuNPs in cancer therapy [25].

Colloidal gold was first reported by Paciotti and his co-workers In 2004 as a delivery vehicle [21].

AuNPs surface was fabricated with tumor necrosis factor (TNF) by them to deliver TNF to the tumor tissue grown in mice. Au-TNF complex was found to have greater tumor accumulation as well as shown lower toxicity to normal cells than TNF [21].

After that AuNPs was explored deeply as a drug delivery vehicle. Many studies have reported AuNPs as drug delivery vehicle for different anticancer/antitumor medicines (Table 1), which include compounds synthesized and derived from plants [23], peptides [24] and coordination compounds [26]. These antitumor molecules have cytotoxic or regulating effects on cancer cells but some drawbacks such as low solubility, short half-life, the development of drug resistance and weak tumor selectivity limit their practical applications. One of the effective approaches is to conjugate the anticancer molecules to nanoparticles, particularly AuNPs with a "hard" core.

One of the most frequently used drugs as anticancer agent is Doxorubicin (DOX) but it is found that it induce high drug resistance in tumor tissue. In some studies, DOX could bind with stabilizer-modified AuNPs via either covalent or non-covalent interactions [30].

Different assays recommended that conjugation favored the intracellular accumulation of the DOX in drug-resistant cancer cells, indicating the chance of bypassing drug resistance in the case of conjugation.

Different internalization mechanisms could be involved in the mechanism by which drug resistance could be avoided by nanoparticle-mediated conjugation. The internalization

mechanism of free DOX is different compared with the conjugated DOX that enter cells by endocytosis approach, avoiding P glycoprotein related drug resistance, as it was suggested by Wojcik et al 5-fluorouracil (5-FU) is another powerful antineoplastic drug, whose highly polar nature limits its topical use in the treatment of skin cancer. Delivery of 5-FU by cetyltrimethylammonium bromide (CTAB)-stabilized AuNPs could gain about 2-fold higher skin permeability compared with the free 5-FU formulation and achieve 6.8- and 18.4-fold lower tumor volume compared with the negative group [31].

It showed that linking hydrophilic drugs to AuNPs can help to enhance in the skin permeability and subsequent drug efficiency against skin cancer. This may have something to do with the use of stabilizer CTAB with positive charge [32]. It should be kept in mind that stabilizers or spacers seem not to be essential in the structure of the conjugated materials. Most of the drugs having carboxylic groups i.e. methotrexate (MTX) can directly link with AuNPs [33]. Free MTX showed low anticancer activity than a very low loaded conjugate of MTX_AuNPs at an equal dose [33]. Which clearly indicate that conjugation of MTX with AuNPs significantly increase the anticancer activity of MTX.

Nucleic Acid Delivery

The use of external DNA and RNA in Gene therapy is an ideal method to treat and prevent cancer. Nucleic acid drugs are highly labile than small molecule medicine. On the one hand, the nucleic acid drugs are susceptible to many environmental risks, such as enzymatic, chemical and physical degradation during gene handling and gene transfection [34]. On the other hand, such drugs

Table 1. Different AuNPs complexes and their anticancer activities.

Anticancer drug	Modifying compound	Nanom-arterial	Cell line	Outcomes	Mode of activity	Ref.
DOX	PEC	DOX-PEC-AuNPs	HepG2	Efficient activity than free DOX	Targeted delivery of DOX to hepatocarcinoma cells	[27]
DTX	HA and GFLGC	DTX@HA-clAuNPs	HeLa and MCF-7 cells	Higher cytotoxicity and tumor inhibition efficacy than free DTX under near-infrared laser irradiation	Targeted anticancer therapy in combination with laser treatment	[28]
5-FU	PEG and FA	AuNPs-PEG5-FU-FA	M139 and M213 cells	Higher cytotoxic effects as compared to free 5-FU and FA	Targeted delivery of 5-FU and targeted therapy of cholangiocarcinoma cells	[29]
LIN	CALNN and GSH	LIN-AuNPsCALNN	MCF-7 cells	Higher antioxidant activity and anticancer activity as compared to Linalool and AuNPs alone	Human breast cancer therapy	[23]
K	-	K-AuNPs	MCF-7 cells	Higher cell apoptosis, antiproliferative ability and inhibition of angiogenesis compared to pure kaempferol	Human breast cancer therapy	[22]

as biologic agents are prone to immunogenicity and are consumed readily by innate immune cells. Therefore, ideal delivery tools are needed to transport such drugs into cells, to prevent nucleic acid drugs from degradation and have a better transfection effect [35]. Now a days, viral vector systems are incredibly accepted for gene transportation but can trigger the host's immune response, which minimize effectiveness of future gene therapy. On the other hand delivery of nucleic acids by non-viral vectors systems, such as AuNPs don't produce such a problem. In contrast to viral vectors, surface design of AuNPs is more flexible, which aids in functionalization and biocompatibility in the body [36]. Moreover, AuNPs can protect nucleic acid from nuclease degradation and physical damage [34] and show more than 99% cellular uptake in spite of surface negative charge [37]. As a result of the above properties, AuNPs conjugated with nucleic acid can be used for gene silencing therapy in tumor model.

For example, Tunc et al embedded morpholino antisense oligonucleotides into a DNA-tile-AuNPs structure for treatment of breast cancer. They found that the DNA-tile-AuNPs structure delivered morpholinos and silenced the expression of HER2 and ERa gene in breast cancer cells more effectively than the liposome-based system [38]. Besides, due to the photothermal effect of AuNPs, the conjugate has the ability to become a dual functional delivery nanoplatform that achieves simultaneously gene silencing and photothermal therapy [39]. The complex still has a good photothermal effect even after nucleic acid functionalization. The composite significantly inhibited tumor growth without overt side effects for major organs after laser exposure [40]. Furthermore, AuNPs can load simultaneously gene and chemotherapy drugs to achieve a synergistic effect. Huang et al prepared a multifunctional nanoplatform based on AuNPs, which co-delivered DOX and microRNA-122, hence achieved triple therapy (gene therapy photothermal therapy and chemotherapy). With the aid of polyethylene glycol (PEG) and HA, this delivery system could selectively target hepatoma carcinoma cells without toxicity to the main organs and showed a better antitumor effect than any single therapy [41]. The release of DNA from the gold nanocomplex can be triggered by exogenous light. Upon laser irradiation, the heat generated by AuNPs through the photothermal effect is transmitted to the ambient DNA molecules. When the temperature reaches the threshold, the chemical linkages break, thus leading to DNA release [42].

Interestingly, the specific DNA release mechanisms induced by continuous wave (CW) versus pulsed lasers are different. Upon CW laser irradiation, high temperature results in dehybridization between double-stranded DNA (dsDNA) and release of nonthiolated ssDNA, while upon pulsed laser illumination, the entire DNA molecules are liberated through Au-S bond cleavage [43]. The incongruity in release mechanism makes cell mortality rate different. In a work, an anticancer drug docetaxel (DTX) was inset into complementary dsDNA that was first attached to gold nanoshells (silica core) through the Au-thiol bond for the treatment of breast cancer. The CW laser-induced DTX release caused a significant increase in breast cancer cell death, while the pulsed laser-induced drug release resulted in unobvious cell death [44]. Accordingly, AuNPs can be used as a promising genetic drug delivery vector, achieving multifunctional anti-cancer therapy.

Challenges of AuNPs in Clinical assessments

Although the preclinical and first medical studies are stirring but there are still numerous main issues that have to be fully clarified earlier to clinical use of AuNPs. It is claimed that cytotoxicity is the most vital problem amongst them. in spite of many assays showing that AuNPs were comparatively low toxic due to chemical inertness of metal gold [45], the toxicity produced by AuNPs

have been demonstrated in multiple cell and animal models. Many factors, no doubt, are able to greatly influence their biodistribution in vivo and ultimate toxicity, such as fundamental features of particles (eg, particle size, shape, surface charge, and coating), experimental conditions (eg, cell and animal model tested, assessed duration), administration scheme (eg, administration route, dose and times) and so onwards. Thereby, the results may be different and even conflicting sometimes. This, along with the heterogeneity among individual tissues and cells, makes it intricate and challenging to utterly comprehend their interplay with the living organisms. Hence, toxicity profile of AuNPs and other reasons decelerating clinical translation of the AuNPs will be described fully in this part. Particle size has been reported to impact toxicity of AuNPs, wherein smaller particles were observed to be more toxic than the larger ones [46]. This may be attributed to the fact that small nanoparticles cross the cell membrane and the nucleus pore more easily, thus favoring the intracellular ROS generation and DNA damage [47]. However, at a more early time point, Chen et al found that AuNPs of 8-37 nm induced severe disease in BALB/C mice after the AuNPs were injected intraperitoneally, while AuNPs of 3, 5, 50, and 100 nm did not exhibit deleterious effects [48].

The results may be related to urinary elimination and excretion since particles smaller than 5.5 nm can be removed rapidly and efficiently through urinary system from the body [49]. Particle shape is equally thought to be an important factor in affecting AuNP toxicity. Comparative toxicity analysis among various shaped AuNPs has already been established. Nevertheless, opinions differ in the shape effect of nanoparticles on cells. In the view of Patibandla et al, AuNRs have more deleterious effects on zebrafish than spherical AuNPs [50]. They attributed the toxicity of AuNRs to CTAB coating, which is an essential but toxic surfactant for the synthesis of AuNRs [51]. Thus, the toxicity of AuNRs can be improved by coating them with alternative biocompatible materials, such as phosphatidylcholine and PEG1 [52], underlining the impact of surface coating materials on toxicity. However, Tarantola et al pointed out that spherical AuNPs are more toxic than rod-shaped particles due to the larger surface area ratio of spherical particles and thus higher intracellular gold content [53]. In other studies, it was observed that non-spherical (star/flower-shaped) AuNPs had relatively stronger toxicity than spherical AuNPs [54]. They attributed this outcome to the larger specific surface area presented by non-spherical AuNPs than spherical AuNPs. Higher is the internalization, more is the harmful substances carried into cells and severer is the cell damage. However, in another study, spherical and rod-shaped nanoparticles were observed to be more toxic than star-, flower- and prismshaped AuNPs [55].

Conclusion

It is concluded that AuNPs based nanomaterials could be used efficiently as a drug delivery vehicle, imaging agents and Phtothermal agents in cancer therapy. In spite of all of these studies still more assessments are required to be done to use Au based nanomaterials/nanomedicine publically. It is expected that AuNPs based nanomaterials could be of great importance and would be an efficient therapeutic agent in oncology.

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Ethical policy

Not applicable.

Author contributions

Mater H. Mahnashia and Bander A. Alyami wrote the paper, Yahya S. Alqahtani and Qipeng Yuan managed the references and Arif Ullah Khan edited the manuscript.

Competing interests

The author declares that there are no conflicts of interest.

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