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A REVIEW OF GOLD NANOPARTICLES IN CANCER THERAPY

[1]K. SIVARANJANI*, [2]M. VETRIVEL RAJAN, [2]R. ROBIN JIYO, [3]M. HARI SANKERJI, DR.M.RAJESH

[1]Assistant professor,[2,3] M.Pharm,

[1]Depertament of pharmaceutics, [2]Department of pharmaceutics, [3] Department of pharmaceutical analysis

Sankaralingam Bhuvaneswari College of Pharmacy, 3/77- C, Anaikuttam Road- 626130

ABSTRACT: Gold is a multifunctional material that has been utilized in medicinal applications for centuries because it has been recognized for its bacteriostatic, anticorrosive, and antioxidative properties. Modern medicine makes routine, conventional use of gold and has even developed more advanced applications. It has been shown that colloidal gold exhibits localized plasmon surface resonance (LPSR), meaning that gold nanoparticles can absorb light at specific wavelengths, resulting in photoacoustic and photothermal properties, making them potentially useful for hyperthermic cancer treatments and medical imaging applications. Modifying gold nanoparticle shape and size can change their LPSR photochemical activities, thereby also altering their photothermal and photoacoustic properties, allowing for the utilization of different wavelengths of light, such as light in the near-infrared spectrum. By manufacturing gold in a nanoscale format, it is possible to passively distribute the material through the body, where it can localize in tumors and be safely excreted through the urinary system. The possibility to modify the surface of nanogold particles with different targeting and functional compounds significantly broadens the range of their potential biomedical applications, with particular emphasis on cancer treatment. Functionalized gold nanoparticles exhibit good biocompatibility and controllable biodistribution patterns, which make them particularly fine candidates for the basis of innovative therapies. In this paper, we give a quick review of the structure, applications, recent advancements, and potential future directions for the utilization of gold nanoparticles in cancer therapeutics.

KEYWORDS: Gold nanoparticles, cancer therapy, Sorption, Conjugation, Photothermal therapy.

1. INTRODUCTION

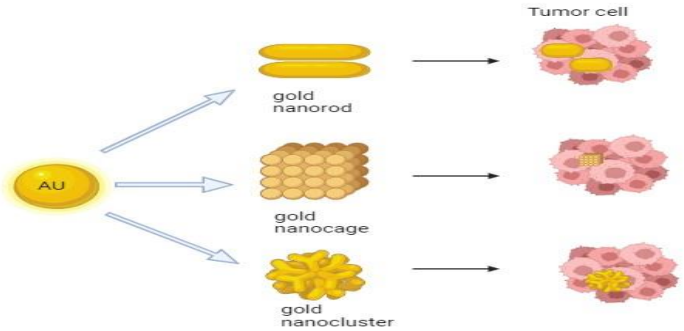
Gold nanoparticles (Au NPs) are effective radiosensitizers in medical applications such as drug delivery and cancer therapy. In biomedical and cancer therapy applications, AuNPs can act as a contrast agent and dose enhancer in image-guided nanoparticle-enhanced radiotherapy using kilovoltage cone-beam computed tomography. The size of NPs is generally below 100 nm and they have low melting points, high chemical reactivity, and large external surface area. Considering the high amount of scientific data on nanogold, this review summarizes recent advances in the field of medical application of gold nanoparticles for the therapy of cancer. [1,2]

1.1 SIZE AND SURFACE CHARACTERISTICS OF NANOPARTICLES

Nanoparticles must have the ability to remain in the bloodstream for a considerable time without being eliminated for effective delivery of the drug to the targeted tumor tissue. Conventional surface particles and non-modified nanoparticles are usually caught in circulation by the reticuloendothelial system, such as the liver and the spleen, depending on their size and surface characteristics. The fate of injected nanoparticles can be controlled by adjusting their size and surface characteristics. Surface characteristics. Surface characteristics of nanoparticles are an important factor for determining their lifespan and destiny during circulation relating to their capture by macrophages. Ideally, nanoparticles should have hydrophilic surfaces so that they can escape macrophage capture. This can be achieved by two methods, first coating the surface of nanoparticles with a hydrophilic polymer, such as Peg, second, protects them from opsonization by repelling plasma proteins; alternatively, nanoparticles can be formed from block copolymers with hydrophilic and hydrophobic domains. Size. In addition to their surface characteristics, there is also one more advantage of nanoparticles is that their size can be adjusted. The size of nanoparticles used in a drug delivery system should be small enough to escape capture by fixed macrophages that are lodged in the reticuloendothelial system, such as the liver and spleen but should be large enough to prevent their rapid leakage into blood capillaries. The size of the sinusoid in the spleen and fenestra of chauffer cells in the liver varies from 150 to 200 nm and the size of the gap junction between endothelial cells of the leaky tumor vasculature may vary from 100 to 600 nm. Thus, the size of nanoparticles should be up to 100 nm to Size and surface characteristics of nanoparticles Nanoparticles must have the ability to remain in the bloodstream for a considerable time without being eliminated for effective delivery of drugs to the targeted tumor tissue. [3,4,5]

2 GNPs WITH DIFFERENT STRUCTURE

Fig 1. Different types of gold nanoparticles



In 1857, Michael Faraday discovered the light-scattering properties of suspended gold microparticles, which is now known as the Faraday-Tyndall effect. Fifty years later, Hirsh et al. found that GNPs irradiated with an electromagnetic wavelength at 820 nm were able to increase the surrounding temperature, which could be used for the treatment of solid tumors. In July 2019, the U.S. Food and Drug Administration (FDA) approved an oral drug based on GNPs, for the treatment of amyotrophic lateral sclerosis (ALS). This demonstrated that GNPs are a safe and reliable tool with great potential for disease treatment. The polarization of free electrons

and the distribution of surface charges are determined by size. GNPs are synthesized in various morphologies, shifting the absorption/scattering peak to the near-infrared window, allowing GNPs in the deep tissue to receive incident light energy. Over the last 20 years, many studies have reported GNPs of various shapes, including nanoclusters, nanorods, nanoplates, nanoshells, nanocages, and nanostars, which have been widely studied in various cancers. In particular, gold nanorods, nanocages, and nanoclusters have been extensively used in gastrointestinal cancer.[6,7,8]

2. GOLD NANOPARTICLES FOR EFFICIENT CANCER THERAPY

Gold nanoparticles (GNPs) have been investigated in the context of various cancer therapies and are sought after as a potential alternative or adjunct to many non-selective chemotherapeutic agents as a means by which to improve therapeutic outcomes while reducing undesirable side effects. The efficacy of plasmonic gold nanoparticles for the thermo-ablation of various cell types has been demonstrated in multiple studies. The efficacy of gold nanoparticles for the thermal-mediated induction of cellular death was demonstrated, wherein anti-CD8-labeled GNPs were used for the selective targeting and destruction of T-cells. [9]

2.1 GOLD NANOPARTICLE SYNTHESIS

Gold nanoparticles are synthesized via either physical or chemical approaches wherein either a bottom-up or top-down approach is taken. Bottom-up methods typically involve the nucleation of gold on top of smaller structures using either chemical, electro-chemical, or thermal reduction techniques.

The most commonly used of the bottom-up techniques is the Turkevich and Brust method, wherein metal salts are reduced to produce spherical, monodisperse GNPs around 10–20 nm in diameter. Sodium citrate salts are commonly used to serve as both a reducing agent and stabilizer that acts to prevent GNP aggregation during synthesis. Instead of citrate, ascorbic acid, amino acids, and UV light have all been used as reducing agents. Schiffrin-Brust is an early, two-phase procedure employing tetrabutylammonium bromide (TOAB) to transfer gold from organic to inorganic solutions, enabling the synthesis of GNPs in organic solutions with high stability. Using this method, GNPs ranging from 2 to 6 nm in diameter can be synthesized. [10]

The most commonly employed Top-down techniques usually create nanoscale materials through the processing of larger macroscale structures via techniques such as lithography. Other commonly employed physical synthesis methods include sonochemical, microwave, and photochemical-based methods. A recently developed technique utilizes N-cholyl-L-valine (NaValC) as a self-reducing and stabilizing agent intended to be coupled with natural sunlight irradiation for the synthesis of GNPs. By modifying the ratio of Au^{3+} to NaValC ions, the amount of sunlight irradiation, pH, and the reaction time, the size and shape of synthesized GNPs can be changed.

Recently, a new fabrication method was developed in which aqueous [$AuCl_4$] can be irradiated with 532 nm nanosecond laser pulses to produce monodisperse 5 nm GNPs without the utilization of capping agents or additives, eliminating the possibility of contamination by residual chemicals. Five hundred and thirty-two-nanometer nanosecond laser irradiation results in a more uniform monodisperse of 5 nm diameter GNPs

compared to older methods using 800 nm femtosecond laser irradiation, which generally results in the growth of nanoparticles as large as 40 nm. [11,12]

2.3 APPLICATION OF GNPs IN CANCER DIAGNOSIS

Precise detection of tumor location and depth in patients is required for successful cancer treatment. Currently, imaging systems, such as computed tomography (CT) and nuclear magnetic resonance (MRI), are used for the clinical diagnosis and treatment of cancers. The GNPs are stable, nonimmunogenic and low toxicity *in vivo*. In addition, they can accumulate in the tumor sites due to the EPR effect so they are attractive in imaging diagnosis. Traditional CT contrast agents are small molecular iodine-based compounds with short circulation time and side effects, such as vomiting and itching, that limit their widespread use. GNPs are a promising CT contrast agent due to their high x-ray attenuation coefficient and biocompatibility. A monoclonal antibody to HSP70 conjugated to GNPs was able to target mouse colon cancer cells and act as a CT contrast agent, displaying remarkable imaging ability in spectral CT and high sensitivity for the detection of even single cells. The Ac-PE-AuNPs were developed with favorable biocompatible. and remarkable X-ray attenuation property, which can accumulate in normal liver than in necrosis regions caused by HCC. It can serve as a negative CT imaging agent that provides a novel diagnostic method for HCC. MRI is a non-invasive imaging modality that is preferred to be applied in soft tissue imaging due to its optimal tissue contrast resolution and multiplanarity. The GNPs are often conjugated with T1 or T2 contrast agents to make them applied in MR imaging. For instance, the gold shell conjugated with the superparamagnetic Fe_2O_3 could enhance the R2 values that can get high-resolution T2*-weighted images to depict individual PANC-1 cell positions. The Fe3O4@Au@β-CD was developed with a low r2/r1 ratio and could be a potential T2 contrast agent for MRI. Moreover, it can target gastric cancer cells and exhibit red fluorescence, which holds remarkable application potential diagnosis and treatment of gastric cancer. Furthermore, the detection sensitivity of gold nanoclusters was enhanced by utilizing the microneedles and the ultrasound to enhance the transparent efficiency, which increased the optical coherence tomography contrast level to identify the early neoplasia. [13]

3. DRUG DELIVERY

The ability to customize AuNPs makes it possible to create particles of various core diameters with complete control over size dispersion. Owing to the high surface area to volume ratio, dense loading of ligands with multiple functions involved in therapy, diagnosis, and targeting can be anchored to the surface of AuNPs. There are two main types of anchoring of drugs to the surface of nanoparticles:

1. Conjugation (attachment to the surface of a nanoparticle through linker molecules);
2. Sorption (fixation on the surface due to non-covalent bonds and the developed surface of nanoparticles).

Hostetler et al. demonstrated the covalent conjugation of almost 100 molecules with one AuNP with a core diameter of 2 nm. In addition, the delicate surface treatment of AuNPs with different multifunctional monolayers provides ideal functional diversity, making them a versatile platform for drug delivery. [14]

The most efficient cellular uptake occurs for particles ranging in size from 25 to 50 nm. In addition, a study on the in vivo uptake of AuNPs and their passive accumulation in the tumor showed that the penetration of nanoparticles through the interstitial space of a tumor is highly size-dependent. While the larger AuNPs accumulate near the vasculature, the smaller AuNPs rapidly diffuse from the vasculature and are distributed throughout the tumor matrix. (15)

There are two main types of targeted drug delivery:

1. Passive transfer (delivery is carried out in areas of increased permeability, which cancer cells often have);
2. Active transfer (accumulation in the tumor due to the binding of a specific ligand and a damage marker).

A critical factor in drug delivery is the EPR effect, which occurs because of the extravasation of macromolecules or nanoparticles through the tumor's blood vessels. Nanoprobe delivery based on the EPR effect is also helpful for tumor imaging agents using fluorescent or radio nuclei in nanoprobes. (15)

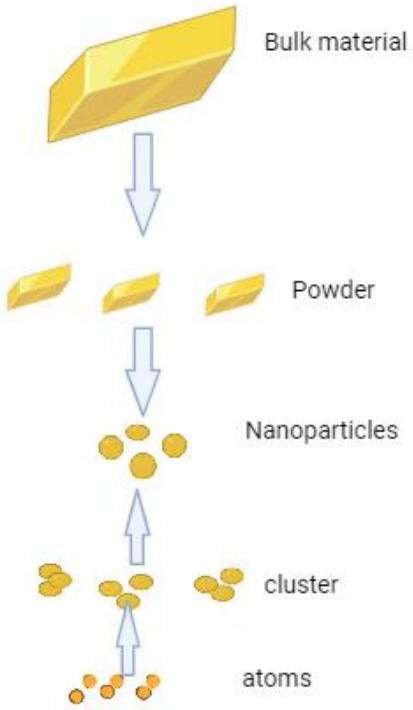
Several researchers have confirmed that extravasation through EPR does not have a reverse mechanism, so an object penetrating inside is delayed for a long time. Currently, there are some mechanisms aimed at improving the EPR effect and the treatment's effectiveness; one of them is a combination of pharmacological and physical methods of treatment.

4. SYNTHESIS OF GOLD NANOPARTICLES

There are two approaches to the manufacturing of nanomaterials:

1. The "top-down" approach, involves the breaking down of large pieces of material to generate the required nanostructures from them.

Fig.2. Synthesis process of gold nanoparticles



2. The "bottom-up" approach, which implies assembling single atoms and molecules into larger nanostructures [1]

4.1 AuNPs BIOSYNTHESIS MECHANISM

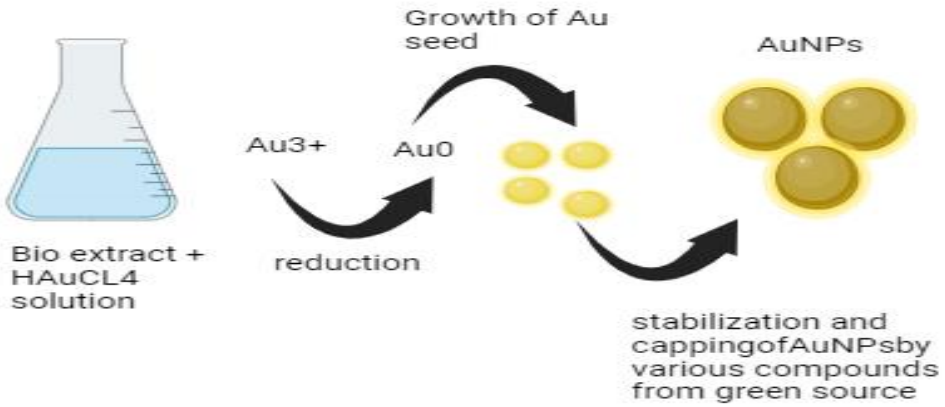


Fig.3. AuNPs Biosynthesis Mechanism

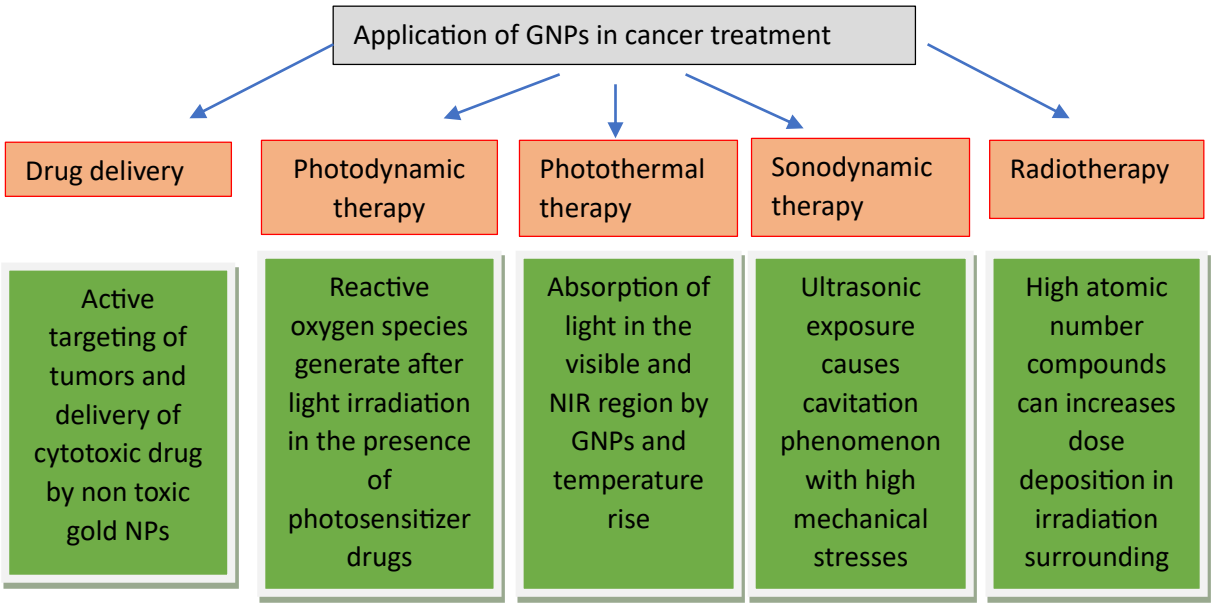
The mechanism of AuNPs biosynthesis is a simple two-step process and does not require a dramatic increase in temperature and pressure. In the first step, the biological extract (e.g., plant, bacterial, or fungal extract) is mixed with the HAuCl4 salt solution, which causes the reduction of gold (Au3+) ions to gold atoms (Au0). In the second step, growth and stabilization result in the AuNPs formation. Finally, the color change of the resulting solution indicates the formation of AuNPs [23,24]. The chemical reactions involved in the reduction of Au3+ to Au0 in the presence of H2O molecules are expressed in the below reactions [17]

Dissociation: HAuCl4 (Chloroauric acid) H2O −−→ H+ + Au3+ + 4Cl−,

Oxidation: 4Cl− −→ 2Cl2 + 4e−,

Reduction: Au3+ + 4e− −→ Au0 + e−.

5. APPLICATIONS



Because of their unique optical as well as surface modification properties, AuNPs have enormous potential in cancer treatments such as PPT, PDT, radiotherapy, chemotherapy, and drug delivery, as explained. [18]

6. PHOTOTHERMAL THERAPY

Photothermal therapy (PTT) is one of the non-surgical methods based on the use of particular photosensitizing substances, which selectively accumulate in pathologic cells and increase their sensitivity to light. Photothermal therapy has several advantages over other methods, for example, high efficiency in the treatment of skin cancer, the absence of complicated procedures in preparation for treatment, and the possibility of using it in hard-to-reach places

Usually, PTT is carried out in two stages the introduction of a photosensitizer drug into the tumor area (or vein) and its accumulation in cancer cells, after which the tumor area is irradiated with a laser with a specific wavelength.

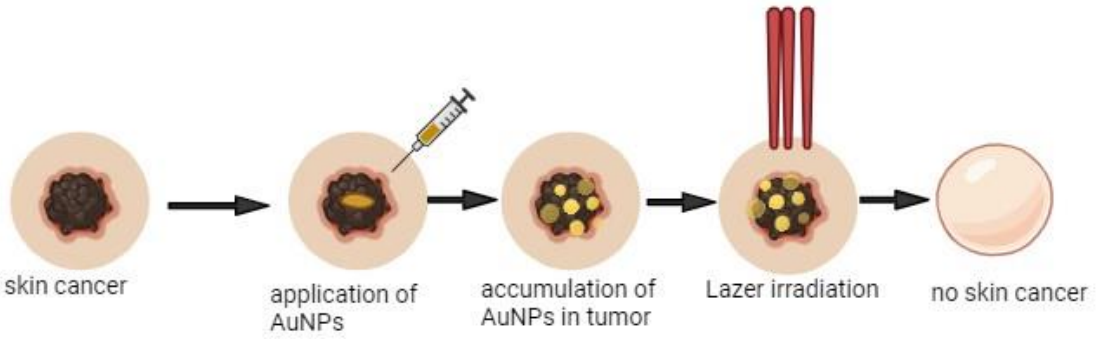


Fig.4. photothermal therapy process

AuNPs actively absorb radiation in the near-infrared range owing to the relative transparency of the human body and its large surface area, and these properties are the reason for the use of AuNPs in PTT. Upon absorption of light energy, the photosensitizer excites the surrounding oxygen molecules into the singlet state, destroying cells by oxidation. Thus, for AuNPs, there is intense heating of cells, followed by their death. The depth of light penetration increases as its spectrum shifts to the red region, so the development of photosensitizers based on metal NPs, including AuNPs, activated by infrared radiation, should increase the depth of the photodynamic effect several times.

An ideal candidate for a photothermal therapy role requires several conditions.

- nanoparticles of suitable size and uniform shape;
- possessing a good dispersibility in aqueous solutions;
- respond to near-infrared light in range (650–950 nm) to prevent damage to surrounding healthy tissue, to ensure sufficient photothermal efficiency, and to ensure enough penetration depth;
- sufficiently photostable to allow adequate diffusion time to reach tumors before losing their light sensitivity;
- exhibit low or no cytotoxicity in living systems.

Gold is already used as a therapeutic method in nanomedicine, with colloidal gold, covalently linked to adenovirus vectors, used to selectively target cancer and induce hyperthermia by near-infrared (NIR) laser radiation. Moreover, gold nanoparticles have several advantages that make them suitable for photothermal cancer treatments.

- The ability to focus on the local region of the tumor while minimizing non-specific distribution;
- They can be activated through near-infrared (NIR) laser light, creating the ability to penetrate deep into biological tissues;
- They can be modulated to create multifaceted drug delivery systems and cancer photothermal therapy.

Several studies have proposed a unique hybrid material based on AuNPs and black phosphorus. Black phosphorus (BP), a new type of two-dimensional nanomaterial, has received serious attention in recent years thanks to its excellent properties and enormous potential in various chemical, physical, and biological fields. The hybrid material is obtained by sonicating black phosphorus suspension, and mixing it in boiling water with a $HAuCl_4$ solution for 2 min. Finally, the solution is centrifuged to obtain gold nanoparticles in black phosphorus (BP-AuNPs). To assess the potential of BP-AuNPs, both in vivo and in vitro experiments showed encouraging results, with BP-AuNPs for 4 h inducing more severe photothermal damage and 75% of cancer cells being destroyed after incubation with 30 μg/mL. Furthermore, the in vivo experiment with 4T1 mammary tumors in mice showed that photothermal treatment of tumors with BP-AuNPs provides high therapeutic efficacy without obvious neoplasms. Thus, the BP-AuNPs have an excellent photothermal effect and high antitumor activity, indicating their promising biomedicine potential.

AuNPs can also be used to increase the sensitivity of tumor cells to hyperthermia treatment, as proven by the work of Moradi S. et al. They analyzed the viability of Y79 cells 48 h after 0.5–11 min hyperthermia with and without AuNPs using MTT analysis and found that the percentage of cell viability was 50% after hyperthermia with AuNPs for 4.5 min; to achieve a similar effect without nanoparticles, it took 9 min. Thus, proving that AuNPs help increase tumor cells' sensitivity to hyperthermia treatment.

Another latest advancement in the hyperthermal treatment of tumor diseases was Fe_3O_4 nanoparticles coated with gold and silver shells. Colloidal solutions of magnetite nanoparticles coated with gold and silver with 10–20 nm had a cytotoxic effect on HCT116 cells. Concentrations of 400 μg/mL and 600 μg/mL of the Fe_3O_4 core with a shell of AuNPs led to a decrease in viability by about 40% and 55%, respectively. [19,20]

7. SONOCHEMICAL THERAPY

In recent years, scientists have widely explored various approaches in cancer therapy based on the action of ultrasound waves on the tumor. There are a few studies on the use of ultrasound techniques in cancer control. The therapeutic effect of ultrasound is based on its interaction with tissues, causing some biological effects.

There are three main methods of ultrasound therapy for tumor disease. high-intensity focused ultrasound (HIFU), low-intensity ultrasound (LIU), and sonodynamic therapy (SDT). The biological effects of ultrasound are mainly caused by heat, mechanical stress, and cavitation. Inertial cavitation is considered a more promising method of using ultrasound therapy as it does not cause thermal effects.

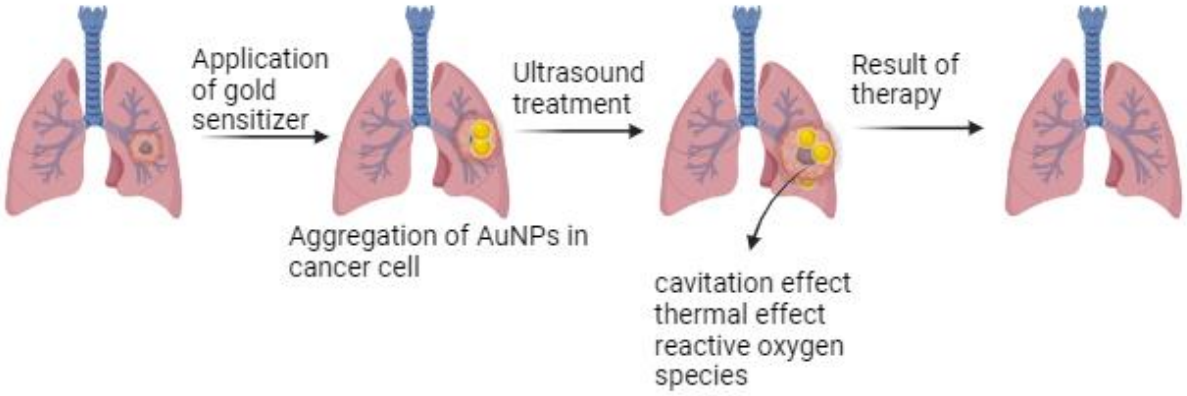


Fig.5. Sonochemical Therapy Process

The main application of nanoparticles in ultrasound therapy for cancer is reduced to the formation of bubbles on their rough surface, which causes evaporation in the environment and, thereby, vapor cavities. The method of sonodynamic therapy seems to be very attractive because, owing to the high penetrating ability of ultrasound (up to tens of centimeters, depending on the frequency), it allows acting on intensely localized tumors that are inaccessible for photodynamic therapy.

Sonodynamic therapy uses the synergistic effect of a non-toxic and selective agent (sensitizer). AuNPs can have tremendous therapeutic effects, together with SDT, through biocompatibility, selectivity, and biodistribution. An example of ultrasound therapy and AuNPs is the recovery after anti-cancer therapy involving active forms of oxygen-ROS. Victor et al. demonstrated that nanoparticles and therapeutic pulsed ultrasound reduce the content of pro-inflammatory cytokines in tissues. During the inflammatory phase of the healing process, ultrasound can activate immune cells to migrate to the injury site. At the same time, gold compounds can suppress the expression of NF-κB and other inflammatory responses. AuNPs can play a positive role after therapy with ROS participation, because, in combination with pulsed ultrasound, they reduce the effect of reactive oxidative forms on damaged tissues, thereby reducing the structural damage caused by this effect.

Beik et al. compared the pine-sensitizing effect of nanographene oxide and AuNPs. They noted that the ultrasound-induced heating of AuNPs was much higher than that of nanographene, which, in combination with vectors that can direct the nanoparticle to the tumor (for example, folic acid and peptide vectors), are promising for targeted sonodynamic therapy.[21,22,23,24,25]

8. TOXICITY: SAFETY TEST

Currently, there are several standard methods for assessing the toxicity/safety of nanoparticles in vitro. In addition, researchers have developed recommendations for determining the toxicity of various nanoparticles. However, these techniques are individual for each type of nanoparticle and cannot be applied to more complex or hybrid materials. This leads to uncertain and unpredictable results for real objects, leading to a lack of therapeutic/diagnostic action or being more detrimental to the body. (26,27)

As mentioned in the section on the effect of shape and size on the biological properties of nanoparticles, there are a considerable number of factors affecting the toxicity of nanoparticles (size, shape, surface charge, and capping agents), and this complicates the possibility of developing an appropriate method for determining toxicity. In addition, it was reported that the toxicity does not depend only on the type of nanoparticles, but also on the target. For different tumor cells, the effect of gold nanoparticles occurs at different concentrations. In this regard, it can be concluded that it is necessary to create several universal procedures (similar to GLP) that allow assessing the safety of nanoparticles in each specific case, which will be used for all similar objects around the world (personalized). (29,30)

Adsorption from Physiological Media

Size, developed surface, shape, and charge contribute to the adsorption of the protein on the surface of nanoparticles. Consequently, this leads to a change in physicochemical parameters and, thereby, worsens the therapeutic properties. Therefore, the development of new agents that would modify the surface could help realistically evaluate the properties of nanoparticles by their physicochemical properties. In addition, several delivery methods that consider the formation of the corona protein and allow it to be used for various purposes are being developed. (30)

Pharmacodynamics: Pharmacokinetics

Even though studies on gold nanoparticles are very relevant, there have still not been comprehensive studies on their kinetics, clearance, and biodistribution inside the organism. The lack of studies on the pharmacokinetics of gold nanoparticles inside the human body limits the possibility of the massive use of gold nanoparticles in treating tumor diseases. Analysis of these parameters is complicated by the difficulty of determining nanoparticles' distribution in the organism, as experiments in vivo and in vitro do not give a complete picture of the biodistribution of nanoparticles within the organism. It is important to note that gold nanoparticles are a convenient object for studying inside the organism, compared with other nano-objects, owing to surface plasma resonance and a high extinction coefficient. (31,32)

Low Efficiency

Wilhelm S. et al. studied the nanoparticles' delivery to tumors and found that, on average, only 0.7% of nanoparticles reach the cancer cells, and only in exceptional cases, did nanoparticles reach the tumors in more than 5%. Furthermore, when nanoparticles are injected, the mononuclear phagocytic system (MPS) and the

renal clearance pathway absorb most of the nanoparticles, drastically reducing the effectiveness and harming the MPS organs. (33)

AuNPs as drug delivery agents targeting cancer cells

AuNPs as drug delivery agents can increase the pharmacokinetics of the drug, thereby reducing non-specific side effects and achieving higher doses of targeted drug delivery. A prominent application of AuNPs is using them as vehicles for the delivery of molecules into cells. The payload can be a small molecule drug or a large biomolecule such as a protein, DNA, or RNA.[41] However, various factors need to be considered in designing an effective drug delivery system. The properties of AuNPs, such as their size, charge, and surface chemistry, have been shown to affect their uptake, as well as their subsequent intracellular fate.

Gold nano-conjugated cetuximab and gemcitabine are highly targeted in pancreatic cancer cells with high epidermal growth factor receptor (EGFR) expression. Jiang et al prepared AuNPs with diameters from 2 to 100 nm and coupled them with trastuzumab using a citric acid reduction method. The results suggest that they target human epidermal growth factor receptor-2 (HER-2)-positive SK-BR-3 breast cancer cells. Better targeting is achieved, and cells have an obvious endocytosis effect on AuNPs with a diameter of 40 to 50 nm, while small-diameter AuNPs tend to separate from the cell membrane. Chen et al used AuNPs of approximately 14 nm as the carrier linking with methotrexate (MTX) to study adverse reactions in vitro and anticancer effects in vivo. The results showed that compared with MTX alone, the coupling MTX of AuNPs can be rapidly and efficiently concentrated in tumor cells which significantly reduces the dose-dependent effect of efficacy. Goel et al also conducted a similar study and found that AuNPs can not only deliver drugs but also specifically infrared photothermal damage of tumor cells, which can be combined with near-infrared rays. (34,35)

AuNP application in tumor imaging

The most effective way to improve the prognosis of tumors is early diagnosis. In precision, intensity-modulated radiation therapy, such as 3-dimensional conformal radiation therapy and image-guided radiation therapy, accurate and clear images are important for the delineation of tumor target areas. In recent years, many studies have attempted to use functional imaging to develop tumor radiotherapy plans. Although single photon emission computed tomography (SPECT) and positron emission tomography (PET) have higher sensitivity and specificity in distinguishing tumors from normal tissues, their spatial resolution is poor. High spatial resolution is important in improving the tumor treatment ratio. The commonly used contrast agents are iodine agents, which have a short half-life in the blood (<10 min) and are less tumor-specific. With the rapid development of nanotechnology, the application of multifunctional nanoparticles in medical imaging has become important, such as iron oxide nanoparticles, carbon nanorods, GNPs, and so on. Among these nanomaterials, AuNPs have received increasing attention due to their mature synthesis, stability, and especially high X-ray absorption capacity.

AuNPs are characterized by small size, good biocompatibility, and high atomic number, which means that AuNPs are potentially good contrast agents. At present, there are 2 ways in which AuNPs can target tumor cells: passive or active. Passive targeting uses only the osmotic tension effect (EPR) to converge in tumor tissue to form enhanced imaging. Active targeting is the coupling of AuNPs with tumor-specific targeting agents, such as EGFR monoclonal antibodies, to achieve active targeting of tumor cells by GNP. When the energy exceeds 80 keV, the mass decay of gold is higher than that of iodine, which indicates that gold-nano is more advantageous in development. Rand et al used mixed AuNPs with liver cancer cells and X-ray imaging and found that the liver cancer cell clusters in the gold-nano-mixed group were significantly more potent than the simple liver cancer cells. Using this new technology, tumors with a few millimeters diameter in vivo can be detected, which is of great significance for early diagnosis.[36,37,38]

AuNP application in tumor radio sensitization

The distribution of AuNPs in tissues depends on their parameters, such as size and ability to inactivate tumor cells. Radiation therapy is widely used in almost all types of tumors, such as breast cancer. The rays include X-rays, gamma rays, and high-energy particles. However, radiation therapy is indistinguishable between cancerous and normal tissues. Therefore, reducing normal tissue damage remains a limiting factor in radiation therapy. Herold et al injected 1.9 nm AuNPs into breast cancer model mice and found that the tumor volume was reduced dramatically and the 1-year survival rate was higher after 2 minutes of irradiation (30 Gy). Stern et al injected AuNPs into the tumor site with radiotherapy and found that the tumor volume was significantly smaller and did not significantly expand with time.

Targeting AuNPs is a hotspot of present research. Coupling chemical drugs or some biomacromolecules with AuNPs through chemical methods can play a role in reducing toxicity and increasing efficiency by changing the volume, mass, and charge of AuNPs. Zhang et al constructed PEG-GNP conjugates from PEG using different diameters of AuNPs. By co-culturing with HeLa cells, Zhang et al found that the amount of the conjugates entering cells was much higher than that of pure AuNPs. Khoshgard et al synthesized folate and AuNPs to construct FA-GNP conjugates and co-cultured with HeLa cells with high expression of folate receptors and found that the uptake of FA-GNPs by cells was much higher. Khoshgard et al found that the DEF (dose enhancement factor) co-cultured with FA-GNPs was 1.23 ± 0.09 times that of the simple irradiation group. The results showed that the main uptake site was the cytoplasm, while the uptake of C225-GNPs was much higher.

There is currently no clear conclusion about the mechanism of radio-sensitization of AuNPs. Jain et al co-cultured breast cancer cells with AuNPs under hypoxic, normoxic, and aerobic conditions and irradiated them. The uptake of AuNPs by cells under hypoxic conditions was higher than that under aerobic conditions. Under hypoxic conditions, the proliferation of breast cancer cells is also significantly reduced. AuNPs showed better sensitizing effects under normoxia and moderate hypoxia. However, under the condition of a lack of oxygen, there is no significant sensitization. Yasui et al concluded that AuNPs are mainly deposited in the cytoplasm

and increase the expression of endoplasmic reticulum stress-related proteins by downregulating DNA repair by inhibiting the expression of DNA repair-related proteins and promoting apoptosis.

AuNPs absorb near-infrared rays, which accelerate the tumor temperature rise and can also be used to enhance tumor absorption of X-ray doses. The combination of hyperthermia and radiation therapy is synergistic. When the tumor was heated to 43.5°C with X-ray irradiation for 2 hours, the heat enhancement ratio was 8:1, making hyperthermia one of the most effective radio-sensitizers. However, tumor hyperthermia has certain limitations, such as poor specificity, difficulty in reaching deep tumors, and heat tolerance in the early stages. [39,40]

AuNP application in tumor gene therapy

Gene therapy is a new treatment that began in the late 20th century and provides an ideal way to treat cancer. The targeted introduction of nucleic acids into tumor cells is a key process in gene therapy. Efficient transfection reagents must protect nucleic acids from nuclease degradation, and nucleic acids are released by cells and act in activated and released forms within the nucleus. AuNPs protect the surface of DNA from DNase I degradation. On the 1 hand, due to steric hindrance, the enzyme cannot bind to the DNA on the surface of the particles and is not degraded by the enzyme. On the other hand, a highly concentrated ion concentration around the DNA inhibits the activity of the enzyme. A synthetic non-viral nucleic acid delivery system such as a liposome has a low immunogenicity but in general, has a problem of low delivery efficiency.

AuNPs have a large specific surface area and are easy to modify. They can be used as an ideal transfection reagent by loading a large amount of nucleic acid while regulating surface charge and enhancing water disposability, improving transfection efficiency and reducing toxicity. Mitra et al used epithelial cell adhesion molecule (EpCAM) monoclonal antibody as a targeting ligand and bound it to PEI-modified AuNPs. The results showed that siRNA-loaded AuNPs successfully entered RB cells and significantly reduced their viability. At the same time, control experiments showed that targeted siRNA-AuNPs significantly downregulated the expression of the EpCAM gene in RB cells compared to non-antibody-modified siRNA-AuNPs.

Ghosh et al used cysteamine-modified AuNP-miRNAs, which are 10 to 20 times more efficient than liposomes and can effectively release miRNAs and downregulate the expression of genes. Since the nucleic acid aptamer has a targeting function, it has become a hot spot for anti-tumor research. Ryou et al used AuNPs to deliver RNA ligands specific for β-catenin (which acts as a transcription factor in the nucleus) into HepG2 cells with higher transfection efficiency than liposomes. The results showed that the transcriptional activity of β-catenin in the nucleus was almost completely inhibited, and the mRNA levels of cyclin D and oncogene c-myc were decreased. In addition, they also ligated the RNA aptamer targeting the transcription factor NF-κB p50 to AuNPs. The results indicated that AuNPs could load aptamers into human lung cancer A549 cells and effectively induce apoptosis. [41,42]

Other applications of AuNPs in tumor management

AuNPs can also be used as a stabilizer for other drug carriers, such as liposomes, and at the same time improve their delivery efficiency. The drug is susceptible to leakage in the plasma and other organs which limits its use. Wang et al examined the adsorption of phospholipids by nanoparticles and demonstrated that nanoparticles can induce gelation at the liposome adsorption site. Since 25% of the outer surface of the lipid is occupied by the nanoparticles, the nanoparticle-modified liposome has no obvious leakage within 50 days of the solution.

Yang et al used AuNPs as stabilizers for oil-in-water emulsion droplets. They prepared a net negatively charged oil-in-water emulsion droplet with a particle size below 100 nm. The positively charged AuNPs bind to it via electrostatic interaction and then as a "bridge" to shield the strong repulsion between AuNPs and force. The results showed that the interaction between the AuNP-emulsion and AuNP-transferrin significantly improved the stability of the emulsion droplets.

In addition, AuNPs can also be used to promote the release of drugs. An et al embedded AuNPs in the middle of the bilayer of the liposome and used its photothermal effect to cause phase transition of the liposome bilayer to achieve drug release. (43)

ADVANTAGES

- ✓ Major benefits of gold nanoparticles as drug delivery agents include

  i) ease of synthesis; and ii) surface easily modified to incorporate an array of ligands for multifunctionality such as targeted delivery.
- ✓ Physio-chemical properties of the gold core are ideal for photodynamic therapies, contrast imaging, and thermal ablation.
- ✓ Engineered nanoparticles encompass the capability for early disease detection.
- ✓ Advances in the field require a multidisciplinary approach to realize the therapeutic potential of gold nanoparticles. (44)

9. CONCLUSION

- Au NPs have high potential in cancer therapy and drug delivery applications.
- Even though Au NPs are not being widely used for clinical applications, the research on Au NP-based drug delivery, gene therapy, photothermal therapy, and radiotherapy all show promising results, and they have proven to be potentially viable solutions in the future.
- From the propitious results at present and expected progress in the future, it is certain that Au NPs will continue to play a significant role in improving the biomedical field, such as in drug delivery and cancer therapy.

- However, some limitations on the Au NP application as nanocarriers or radiosensitizers such as cytotoxicity, nonbiodegradability, and the modulation of cellular responses should not be neglected, and need to be investigated in detail.
- Cancer remains the most common cause of death currently. Hence, there is a need to develop new and improved cancer treatment and diagnosis, which requires new and modern approaches, and AuNPs can become one of these new approaches.
- Although there have been several scientific studies on NPs' application in cancer medicine, studies on AuNPs' use in cancer therapy and diagnostics are emerging.
- Therefore, in this review, we analyzed available data on the applications of AuNPs in oncotherapy and cancer diagnostics. Studies have shown that, while shape, size, and charge have a considerable impact on the properties of AuNPs, no direct correlation was found between those parameters and the effectiveness of AuNPs' use in therapy.
- Moreover, for each type of tumor disease, a personalized approach is required to establish the optimal physical and chemical parameters of AuNPs that will ensure maximum efficiency and safety

10. LIST OF ABBREVIATIONS:

LPSR	:	localized plasmon surface resonance
AUNPs	:	Gold nanoparticles
FDA	:	Food and Drug Administration
GNPs	:	Porous gold nanoparticles
PET	:	positron emission tomography
EGFR	:	epidermal growth factor receptor
EPR	:	osmotic tension effect
EPCAM	:	epithelial cell adhesion molecule
CT	:	Computed Tomography Scan
MRI	:	Magnetic resonance imaging

11. REFERENCE

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FIGURE LEGEND

1. **Fig 1. Different types of gold nanoparticles**

   This legend provides a clear reference for understanding the representation of each type of gold nanoparticle and the corresponding ligand interactions with tumor cells depicted in the figure.

2. **Fig 2. Synthesis process of gold nanoparticles**

   This legend provides an overview of various methods employed for synthesizing gold nanoparticles, each offering unique advantages in terms of control over size, shape, and surface properties

3. **Fig 3. AuNPs Biosynthesis Mechanism**

   1. Initial Reduction: The biosynthesis process starts with the reduction of gold ions (Au+) to gold nanoparticles (AuNPs) using a reducing agent such as citrate, tannic acid, or ascorbic acid.

   2. Nucleation: Once reduced, the gold atoms aggregate to form small clusters or nuclei, which serve as the building blocks for the nanoparticles.

   3. Growth: The nuclei continue to grow as more gold ions are reduced and added to the existing clusters. This growth phase is typically controlled by factors such as temperature, pH, and the concentration of the reducing agent.

This legend summarizes the key steps involved in the biosynthesis mechanism of gold nanoparticles (AuNPs), from initial reduction to characterization.

4. Fig 4. Photothermal therapy process

1. Heat beams target cells, ablating with precision, Cancer's grip weakened, with each incision.
2. Light's energy is absorbed; tumors fade away and Photothermal therapy heralds a brighter day.
3. Molecular dance, in the realm of infrared, Destroying malignancy, where it once spread.
4. A beacon of hope, in the fight against disease, Photothermal therapy, bringing healing with ease.

5. Fig 5. Sonochemical Therapy Process

The ultrasound transducer emits high-frequency sound waves into the lung tissue to initiate the sonochemical process. The tumor within the lung tissue is the target for sonochemical therapy. It may be malignant or benign and requires localized treatment to reduce its size or eliminate it.