

Application of gold nanoparticles in cancer diagnosis and therapy: A mini-review

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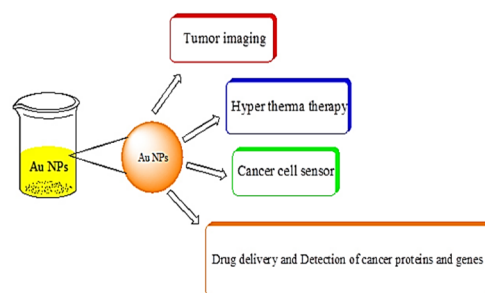
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Abstract

Gold metallic nanoparticles have received a great and well-deserved attention due to their wide application in different fields of scientific and technology, especially biological and therapeutic applications such as cancer diagnosis and treatment according to their advantages including biocompatibility, low toxicity, controlling size and shape, easy synthesis, selective accumulation in cancer cells, high activity, and optical properties. The targeted nanocarriers have given new hope in order to the treatment of this disease all over the world. Understanding the medical effects of gold nanoparticles is a key issue for their rational and efficient design. Regarding this issue, the reported studies indicate that the quality of therapy and identification process of diseases has improved according to gold nanoparticles. It is expected that in the near future, these nanomaterials will provide the most fruitful therapeutic results. With this in mind, this mini-review tries to address new targets for cancer cells, new ways to target based on gold nanoparticles as well as stabilizing nanoparticles locally on cancer cells and the resulting degradation of side effects.



Keywords: Gold, Metallic nanoparticles, Cancer, Nanocarriers.

Introduction

Cancer is the second case of death in the United States¹ and is the second leading cause of death in other countries.² Studies have shown that many deaths in 2000 were reported due to this disease.³ According to the conducted studies, the number of deaths due to cancer is increasing.⁴ Nanotechnology has created a new therapeutic revolution in cancer therapy.⁵ Cancer nanotechnology was first applied by using liposomes and various types of polymers in the mid-1980s.⁶ Today, there are many types of nanotechnology platforms available to explore ways to diagnose cancer. These platforms have a range from 1 - 100 nm that by defined nanoparticles (NPs).⁷⁻¹⁰ Due to its small size, nanoparticles have unique optical,¹¹ magnetic,¹² quantum¹³ and therapeutic¹⁴ properties in comparison to their bulk state. The nanoparticles are used in diagnosis and treatment of cancer including Drug delivery,¹⁵ detections of cancer proteins¹⁶ and genes,¹⁷ tumor imaging,¹⁸ hyperthermia,¹⁹ and sensing studies.^{20,21} Most studies include carbon nanotubes,²² magnetic nanostructure,²³ liposomes,²⁴ mesopores,²⁵ metal nanoparticles²⁶ and so on. Among them, metal nanoparticles (MNs) have attracted much attention in terms of their physical and chemical properties in cancer therapy.²⁶ The most of metal nanoparticles (MNs) that have recently played a key role in treating cancer are Au nanoparticles.²⁷ For several reasons, the use of Au nanoparticles is higher than other metal nanoparticles due to their capabilities including biologically inactive,²⁸ controlling the surface chemistry by various functional groups,²⁹ easy

adjustment of size and shape during synthesis³⁰ and unique optical properties because of the localized surface plasmon resonance (LSPR) phenomenon.¹¹ An interesting example of plasma peak is plasma peak related to pure AuNPs, pure silver, and alloys of Au and Ag that is shown in Figure 1. It is clear from Figure 1 that the plasma peak of the spherical Au and Ag NPs located at 415 and 516 nm.¹¹ These advantages have made them suitable for cancer treatment applications. In this mini-review, different synthesis routes of Au nanostructures including spherical nanoparticles,³¹ nanorods,³² nano cube/cage,^{33,34} and their applications have been investigated in cancer nanotechnology.

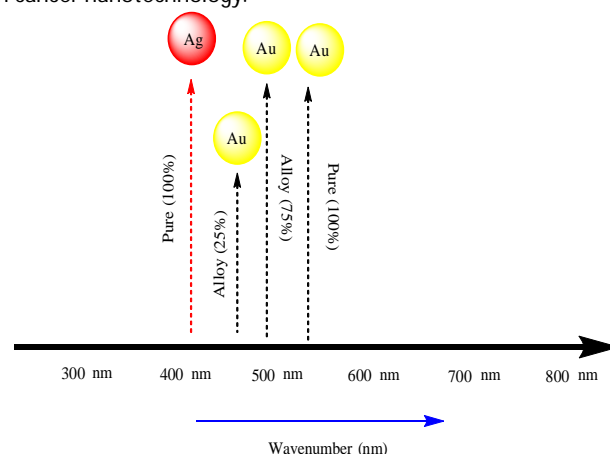


Figure 1. Plasma peak for Ag and Au nanoparticles (alloy and pure) impurities (Reprinted with permission).¹¹

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Synthesis method of spherical Au nanoparticles

The sphere is the simplest shape in the fabrication of Au nanoparticles by reducing the chemical compositions of gold. A common material for the synthesis of these nanoparticles is chloroauric acid (HAuCl_4).³⁵ Nevertheless, Au nanoparticles like any other nanoparticle are agglomerated, and in order to overcome on this challenge, there is a need for capping agents to bind with Au nanoparticles.³⁶ Two methods of Turkevich and two-phase Brust have been reported to synthesis the spherical AuNPs.^{37,38} The particle size obtained by the Turkevich method is about 20 nm, and sodium citrate plays a very important role in this synthesis as a reducing agent and capping agent.^{38,39} In the two-phase Brust method, two organic and aqueous phases are applied so that gold ions are converted to spherical AuNPs in two stages. In the first step, gold ions are usually reduced by thiol (-S-H) ligands as reducing and capping agents, and in the secondary step by sodium borohydride (NaBH_4). On the other hand, to bring the gold ions into the organic phase and to react, it is usually used from a transitional phase which called tetra-octyl ammonium bromide (TOAB).^{38,39} The schematic of synthesis of two-phase Brust is described in Figure 2. The only advantage of this procedure is controlling the particle size by variation of the ratio of gold ions to NaBH_4 .⁴⁰ Yang et al. synthesized the spherical AuNPs by the two-phase Brust method. Their results showed that it could be utilized for therapeutic purposes through modifying the surface of the AuNPs by oleylamine (OAM) and S-H organic groups.⁴¹

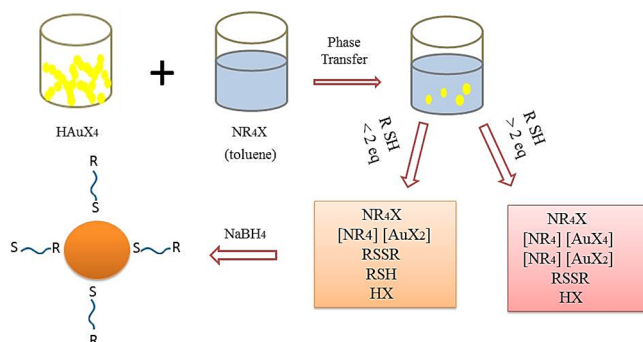


Figure 2. Synthesis of spherical AuNPs with Brust two-phase (Reprinted with permission).⁴⁰

Synthesis method of Au nanorod

The Au nanorod is not as easily synthesized as the Au nanosphere because it requires anisotropic growth, a reaction which does not happen spontaneously.⁴² Several different methods have been used to overcome this issue such as synthesis in templates,⁴³ seed-mediated (SM) growth in solution⁴³ and non-seeded growth⁴³ in solution. Synthesis in templates can be divided into two different classes; synthesis in hard templates (HT)⁴⁴ and synthesis in soft templates (ST).⁴⁵ The nanoparticle is produced either by chemically reducing the gold precursor inside the template pores or by electrochemical deposition of the gold precursor on the templates.⁴⁴ Soft templates are, for instance, rod-like micelles and certain surfactants.⁴⁵ The shape of the rod-like micelle and the specific binding behavior of the surfactants promotes the anisotropic growth of the nanoparticles. Seed-mediated (SM) growth and non-seeded growth are both wet chemistry methods. Recently, Wang et al. have reported the synthesis of Au@Ag core-shell by seed-mediated (SM) growth.⁴⁶ In the SM method, a reducing agent such as ascorbic acid is sufficient for this mechanism, considering the gold seeds operate as a catalyst. In the non-seeded method, the strong reducing agent of NaBH_4 is

commonly used to induce nucleation and a weaker reducing agent is used to promote growth similar to the SM growth method.⁴⁷

Synthesis of nano-cubes/ nano-cages

The most common method to synthesis the AuNCs (nano-cube/nano-cage) is by reducing the gold ions into gold particles which are oxidized through the process, leaving a hollow gold cube. At high concentrations of HAuCl_4 , the nanocubes change to porous nano-cages.⁴⁸ Silver nano-cubes are synthesized by reducing the silver nitrate using NaBH_4 as reducing agent and PVP (poly vinyl pyrrolidone) as capping agent.^{49,50} There are also many methods to synthesize the Au nanocages by the method of the seed-mediated growth. Indeed, one of the important impurities in the seed-mediated synthesis of Au nanorods are AuNCs.⁵¹

Applications of AuNPs

AuNPs have a high potential for detection, improvement, and treatment of cancer. High biodegradability,⁵² selective accumulation in cancer cells,⁵³ and low toxicity⁵⁴ are the most the advantages of these particles. Plentiful studies have been reported on the application of AuNPs in the fields of tumor imaging,⁵⁵ hyperthermia therapy (HTT),⁵⁶ sensors,⁵⁷ and drug delivery,⁵⁸ which are discussed in this section.

Tumor imaging

In recent decades, the use of AuNPs as a valuable and practical tool in the case of tumor imaging has become one of the innovations in this field. Given their extraordinary optical properties,¹¹ these nanoparticles have been developed in imaging tumors. Zhou et. al prepared a polymeric substrate of AuNPs for the imaging of the tumor and blood. Their findings showed that AuNPs are readily distributed in aqueous solution and due to the modification of their surface with PEG are stable in colloidal form. Meanwhile, they are non-toxic and have a successful effect on tumor imaging and blood pools (Figure 3).

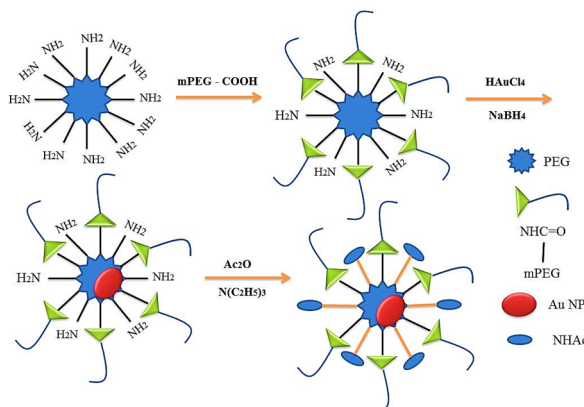


Figure 3. Synthesis schematic of polymeric substrate AuNPs for tumor and blood (Reprinted with permission).⁵⁹

Sung et. al reported the self-assembly of AuNPs modification with a mixture of PEG and polyethylmethacrylate (PEMA) to vesicular macrostructures. The results of this work confirmed the potential of AuNPs in tumor imaging by transmitted electron microscopes (TEM) and scanning electron microscopy (SEM).⁶⁰ Au nanocomposites (NCs) have been manufactured for tumor imaging by the magnetic resonance imaging method. Jane et.al placed the gold layer on the surface of the modified magnetic nanoparticles through the poly(L-histidine) chelate agent, and the advantage of

this study was that the plasmonic characterizations of AuNPs could be controlled in tumor imaging (Figure 4).⁶¹

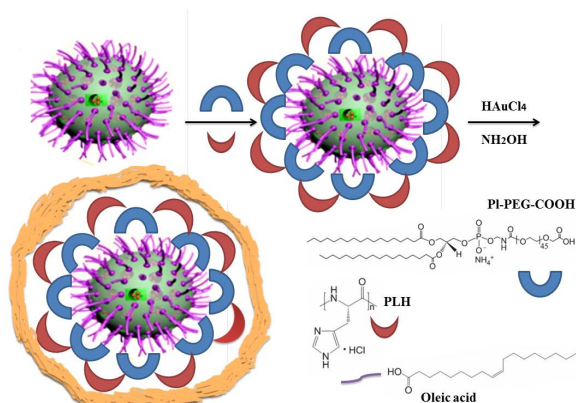


Figure 4. Synthesis of magnetic Au nanocomposite for tumor imaging control purposes (Reprinted with permission).⁶¹

Recently, the application of Au nanoshell and Au nanospheres have been reported in *in vivo* and *in vitro* imaging. Au₃Cu₁ were suggested in the role of contrast agent of blood vessels in *in vivo* imaging.⁶² As the blood-poor, growing tissues or tissues with high metabolism require more blood supply, the body for long-term control of the local bloodstream releases vascular factors, which leads to the creation of the new blood vessels or angiogenesis.⁸³⁻⁸⁶ Regarding this process, it can be said that angiogenesis is closely related to the progression of cancer. In this case, the diagnosis and treatment of the disease are very necessary. On the other hand, it helps researchers in delivering nanoparticles to the tumor tissue as a contrast agent. As presented in Figure 5, endothelial cells in a healthy tissue have a regular and impenetrable space for AuNPs, but in tumor tissue, the arrangement of these cells is irregular and has a large pore.⁸⁷

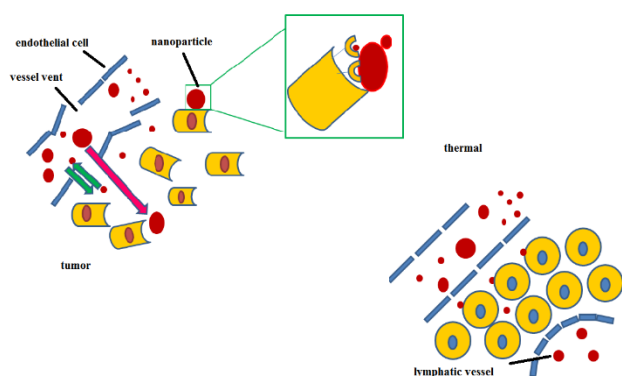


Figure 5. Possibility of transmitted AuNPs from tumor tissue (Reprinted with permission).⁸⁷

HTT (Hyperthermia therapy)

Cancer cells are sensitive to hyperthermia (HT) due to their rapid growth rate and fast metabolism compared to normal cells. In general, there are several methods of transferring energy to heat the tissues of the body, including the use of the electric field, microwave radiation, electromagnetic irradiation, and near-infrared (NIR) light.⁶³ Using the above methods for thermal treatment, the energy distribution is not the same throughout the body, and healthy tissue is damaged around the tumor.⁶⁴ The use of nanostructures as agents that can only accumulate in tumor cells in a specific way, as energy converters, (nanoparticles can convert

irradiated energy into heat in tumor cells) have been highly regarded in recent years.⁶⁵ Gold nanostructures have presented good tools for treating HT with absorbing light in the visible area, NIR, and the rapid production of heat.⁶⁵ These nanomaterials are suitable for HTT due to SPR and lack of irradiation photoluminescence absorption.⁶⁶ Spherical AuNPs absorb the light several times of the organic colors, and nearly 100% of the absorbed light in these structures is turned to heat.⁶⁷ These nanoparticles are every appropriate under radiation and also have high biocompatibility.⁵² Considering sum of these factors and other properties, spherical AuNPs is one of the best choices for photothermal therapy (PTT). Due to the absorption of surface plasmon resonance in the spherical Au nanostructures (wavelength of about 500 nm), their use is limited to superficial cancers such as skin cancers and are not proper for deep cancers.⁶⁵ The first study in this area was conducted in 2003 and the death of cancer cells with pulsed lasers was determined, while around cells that were lacked the nanoparticle and were exposed to laser radiation survived.⁶⁸ In another study by El-Seyyed et al.,⁶⁹ spherical AuNPs (40 nm) were attached to an epidemic growth factor (EGFR) and utilized against head and neck cancers. After 4 minutes of continuous laser irradiation, the death of cancer cells was determined. Researches have shown that intravenous injection of Au nanorod leads to more accumulation in cancer tumors compared with subcutaneous injections, which increases photothermal therapies of Au nanorods.⁷⁰ The results of Bhatia confirmed that injections of PEG-coated nanorods, completely destroyed the cancer cells, and when the mice were examined, tumor growth was not observed.⁷¹

Cancer cell sensor

AuNPs with dimensions of 3 nm to 100 nm, related to their optical and temperature characteristics, are good indicators for the design of biosensors. This molecular detection approach is 100 times more versatile than conventional fluorescence manners.⁷² Studies by Al-Saeed et al. indicated that AuNPs coated with anticancer antibodies can effectively bind to cancer cells. Many of the cancerous cells contain protein in their surface, known as the epidermal growth of receptor. This protein is not observed in healthy human cells.^{73,74} The results reveal that when malignant cells are exposed to laser radiation in the absence of AuNPs, they will not be destroyed.^{73,74} In another study, Tabrizi succeeded to design Nano-biosensor from AuNPs to determine the number of leukemia cells.⁷⁵ According to the findings, compared to previous reports, this Nanobiosensor is inexpensive and has a good selectivity in the separation of Pathogenic cells from the blood.⁷⁴ Chen et al.⁷⁶ developed an AuNPs-based thrombin nanosensor with functionalizing it using fibrinogen. In general, sensors based on AuNPs can be attractive in the next few years for the challenges of current methods to treat cancer.

Drug delivery and detection of cancer proteins and genes

Drug delivery systems (DDS) are applied to improve the pharmaceutical and therapeutic properties of drugs in patients. These systems release the drug at a specific position. Nanoparticles are extensively applied in DDS. In recent years, there is an increasing interest in the preparation of nanostructures as carriers for drug delivery⁷⁷ due to their wide advantages such as the controllable and slow release of the drug material, the protection of the pharmaceutical molecule, the particle size smaller than the cell, the ability to cross biological barriers to carry drug to the target site, increase drug durability in the bloodstream and targeted drug delivery, which these factors increase the therapeutic yield of the

drug. Among the various metallic nanoparticles, AuNPs have been selected as an interesting candidate for delivery of pharmaceutical products.⁷⁷ Non-toxicity of AuNPs, easy synthesis, variability with functionalization and photophysical properties, makes them suitable for drug delivery. It is feasible to combine AuNPs with other nanoparticles and then use this formulation to advance drug delivery goals to eliminate cancer. The researchers proposed a new therapeutic approach by combining nanoparticles of Au, Bacteriophage, and nanocarriers such as liposome and silica.⁷⁸ These phage particles may detect the target molecule on the tumor cells. The AuNPs play the role of reporting agent.⁷⁹ The Nanocarrier also carries the desired drug that can release chemicals through an external stimulus such as heat. In a reported study, heat-sensitive liposomes were applied as carriers. By heating the liposome, the drug is released.⁸⁰ Regarding this subject that AuNPs are important in chemotherapy, releasing these nanoparticles in a tumor is a promising task and will be a prospect for further advances in this field. The main challenge in diagnosis cancer is the estimation of proteins related to a certain tumor. Prostate cancer in men and breast cancer in women are the second cause of deaths due to cancer in the United States.

Scientists have greatly estimated the likelihood of saving the lives of people at an early stage of the disease. For example, scientists in the Northwestern University have developed extra sensitive technology based on Au and DNA nanoparticles that can detect prostate special antigens when it is low in the blood.⁸¹ Bladder cancer one of the five most current cancers in the world. On the other hand, the second most common cause of death in malignant patients is related to the uterine-genital system. Cytology and cystoscopy are traditionally used for patients with this cancer. The low sensitivity of cystoscopic treatment, which is unaggressive, is not responsive to the infected sufferers. In a conducted study by Wu et. al,⁸² researchers developed Au/PL (Poly Lactide)/ITO (indium tin oxide) nanocomposite in order to quickly diagnose this kind of cancer which is ITO a hydrophilic interface for its treatment.⁸² Regarding the above-mentioned studies, scientists by AuNPs hope to diagnosis the tumors and cancers that express certain proteins in the early stages of their formation and resulting decrease in mortality rate by increasing the possibility of treatment.

Conclusion

The conducted studies indicate that there is an increasing tendency toward the use of AuNPs owing to their wide advantage including the selective delivery capability, ease of access, and low toxicity that these advantages allow scientists to detect cancer at early stages within fewer time frames. These nanoparticles can be utilized in medicine for cancer treatment, drug delivery, and biomedical imaging. The development of gold metal nanoparticles will provide special facilities to identify numerous molecular targets together in small tumor samples for the adoption of a therapeutic strategy that will further reduce irreparable risks in the future.

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