

# Applications and Advantages of Gold Nanoparticles as X-Ray Contrast Agent

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## Abstract

A new contrast agent in medical imaging discovered and developed since 10 years ago and it's under study until this moment because the classic contrast agents impose earnest limitations on medical imaging abilities such as the short imaging time, poor contrast X-ray images for obese patients (over weighted patients) and real side effects renal problems and toxicity problems. The new contrast agent is the Gold Nanoparticles (GNP) may overcome these restrictions due to its properties where the (GNP) bio distribution is higher than tri-iodobenzene compounds. also, bone /tissue interference is more clear and obvious than tri-iodobenzene compounds and in general nanoparticles clear the blood slowly than classic contrast agents which permit for longer imaging time and all of that leads to enhancing the X-ray diagnostic. Gold Nanoparticles were injected intraperitoneally into mice then images were taken by conventional X-RAY unit. Tumors were seen clearly.

**Keywords:** Gold nanoparticles; X-ray; Toxicity

## Introduction

Recently the nanoscience is present in Human life, and it has much impact on the areas of health care and medicine. The medical field is complex, so all of the advantages from nanoscience to medicine field will take a long time for being evident. However, other advantages will come promptly. The instruments of research and medical practice are expensive where the excellent results related to accurate tools which proportion to cost. The results of research will participate in birth a new generation of instruments as well as the diagnostics will become, more effective, enabling faster response and the ability to treat new diseases. drugs, Small sensors. Disease indicators and markers, implantable devices, computers, the diagnostic instrument will constantly monitor health, with low cost, and fully automatic processing will be possible. Many new kinds of treatment can be addressed, treating diseases more safely, the medicine cost will be cheaper than before and the benefits will be experienced by much more people around the world [1]. The nanomaterial is that material which has at least one dimension within the Nano range (1 to 100 nanometer). Any material in the nano range will have properties differs from the properties of the same the material in bulk range (more than 100 nm) such as the melting point and photo catalytic and interference with living organs properties and etc. The Gold Nanoparticles (GNP) has excellent properties for *in vivo* usage due to its inert, low toxicity, unique optical, chemical stability and ease to synthesis. The recent contrast agents of X-rays imaging are based on iodine with substituents added to overcome the problem of water solubility.

For example, an ionic form is called "Diatrizoate", was introduced in 1954, but its high osmolality was found to be the source of chemo toxicity [2]. In the 1970s, another non-ionic form which is called "iohexol", lowered osmolality and is still used today widely under the name "Omnipaque" and GE Healthcare. Because osmolality was still too much, a dimeric molecular weight to high molecular weight elements failed due to performance, toxicity, or cost. The iodine contrast agents with low molecular weights (diatrizoate, 613; iohexol, 821; iodixanol, 1550) effect vascular permeation and rapid renal clearance, necessitating short imaging time. Catheterization is therefore required but carries the risks of arterial leakage, myocardial infarction, anaphylactic shock, dislodgement of plaque, stroke, and renal failure. Another important limitation of the iodine-based contrast

agents is in molecular imaging since their combined with antibodies or other targeting moieties fail to deliver iodine to desired locations at detectable concentrations.

So, the usage of (GNP) for X-ray imaging *in vivo* is preferred due to its higher atomic number (gold 79 vs. Iodine, 53), and the absorption coefficient of gold is higher where (at 100 keV: gold: 5.16 cm<sup>2</sup>/ gm; iodine: 1.94 cm<sup>2</sup>/gm; soft tissue: 0.169 cm<sup>2</sup>/gm; and bone: 0.186 cm<sup>2</sup>/ gm), the GNP provides contrast about 2.7 times greater than iodine per unit weight [3]. X-ray Imaging with (GNP) as contrast agent lessen interference from higher bone absorption to lower organs or soft tissue absorption which would minimize radiation dose to the patient. Gadolinium used as contrast agent instead of iodine-based contrast agent to imaging human chest with half of X-ray dose [4]. Perhaps Molecular imaging could be achieved as each nanoparticle like to bound targeting agent (GNP) would deliver gold atoms to a relative receptor that way increasing the information. The gold is expensive more than iodine but significant benefits and low detectable amounts should enable workable gold-mediated clinical radiography. The Intraperitoneal Injection is one of the most frequently used parenteral routes of administration in rats. the abdominal cavity is characterized by its large surface area and its plentiful blood supply and that will facilitate rapid absorption. Absorption from this route is usually one-half to one-quarter as rapid as that from the intravenous route (Woodard, 1965). However, for long-term studies, repeated injections may lead to tissue reaction and adhesions. As relatively considerable volumes can be given Intraperitoneally, as well as the potentially irritant substances, may be diluted. When using this method it has to be kept in mind that substances given intraperitoneally are first absorbed into the portal circulation. So, Biotransformation of the injected substance may

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occur in the liver before it reaches the general blood circulation so its bioavailability is quite different to that of an intravenous injection [5].

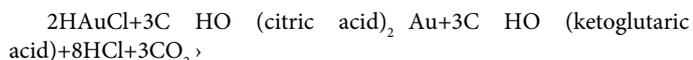
## Materials and Methods

### Animals preparation

The selected animal is a mouse and a group of 20 healthy mice will participate in the experiment. The mice (gender: female) were undergone to the operation of subcutaneous implantation of EMT-6 syngeneic mammary carcinoma cells [6]. After 10 days after tumor initiation, (GNP) were injected via intraperitoneal. Experimental protocols of using animals were approved by the University of Al-Mustansaria / research center of cancer diseases.

### Nanoparticles preparation

The nanoparticles were examined by electron microscopy. The concentration of (GNP) was 0.00346212 gm/ml of Au, and injected volume was 0.01 ml/ gm of mouse weight. (GNP) suspended in distilled water. The synthesis of (GNP) was done by citrate reduction Method [7]. A group of nanoparticles (NP) was synthesized by using various dilutions. The volume of 200  $\mu$ l, 300  $\mu$ l, 400  $\mu$ l, and 500  $\mu$ l was taken from 1% tetra chloroauric acid (with 49% Au) solution and diluted to 50 ml to make 10 mMolarity, 15 mMolarity, 20 mMolarity, and 25 mMolarity, aqueous solutions of tetra chloroauric acid respectively. This solution was heated until the temperature reaches 97°C on a magnetic stirrer, 1.5% trisodium citrate was added in continuous mode with simultaneous to this solution. Stirring. After addition, the stirring continued until the solution convert to brilliant red colored as shown in Figure 1. The synthesis reaction summarized as:



This solution should be stored at 4°C for future use [7].

### X-ray tests

A conventional X-ray unit (Shimadzu Corp., model: Radspeed, serial NO.: 3M5262F3B010) was used with 200 mA and 40 kV and Kodak CR (Model: CR MAX and serial NO.: 7751) and Laser Printer (Model: DV5950 and serial NO.: 59580328) where used for the print of X-ray images. In general most of the mice survive for 7 days after the experiment then they get back to the animal house of the research center of the cancer diseases.

## Results

Gold nanoparticles, 38.5 nm in diameter, were injected via an intraperitoneal into mice bearing EMT-6 syngeneic mammary tumor. The exposure of X-ray imaging time 10 min. after the injection for I.P injection For X-ray imaging, the imaging of I.P shows excellent details after 10 min. only and more distinguished from the near soft tissue as shown in Figure 2. The nanoparticles enable detection, direct imaging, and measurement of tumor real size (2D). The Images were taken at fixed times after intraperitoneal injections show that the (GNP) do not concentrate in the spleen and liver due to its size, clearance and toxicity are effective issues for clinical imaging. Mice intraperitoneally injected with the (GNP) at 2.7 g Au/kg survived over one week without any signs of sickness. The LD50 for this (GNP) is about 3.2 g Au/ kg. The tumor: muscle gold the ratio was 3.4 at 10 min. post injection, improving to 9.6 at 24 h, enabling clear plan of the tumor. In addition to the enhancement of X-ray imaging, due to high absorption of the tumor to X-ray by the assistance of (GNP). the (GNP) play a significant role

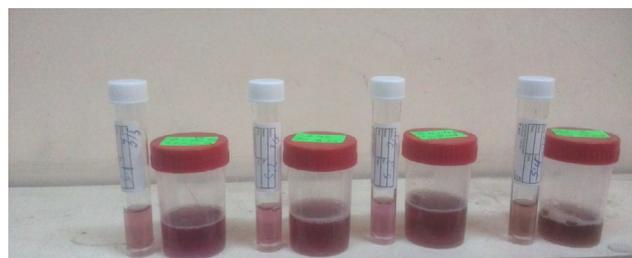


Figure 1: Samples of Gold Nanoparticles.

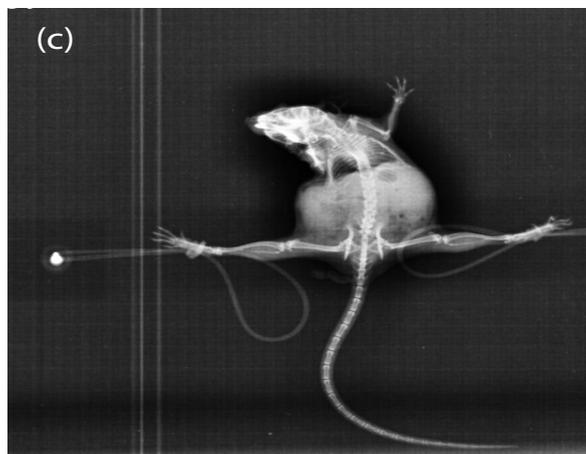
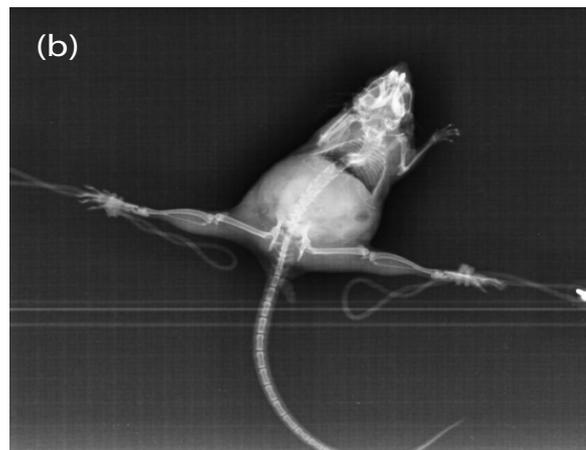


Figure 2: X-ray images for mice. (a) Before injection (b) 10 min. post intraperitoneal injection of rod gold Nanoparticles (c) 10 min. after intraperitoneal injection of spherical gold nanoparticles.

to improve the efficacy of radiotherapy [8]. Even when concentrated; (GNP) solutions were same to water in viscosity while the iodine-based contrast agent needs high viscosity to get sharp contrast. (GNP) can be suspended in water or aqueous buffers easily after a complete dry. No, changes are shown in spectra of (GNP) or aggregation and it still stable after 4 months storage at 22°C.

## Discussion

Gold Nanoparticles is a good X-ray contrast agent and better than the Iodine due to the properties of GNP as the absorption is higher at low energy (40 keV), where X-ray unit operates where (GNP) providing an approximately 3-fold absorption more than iodine. In contrast; To neglect the osmolality difference the (GNP) contains about 250 gold atoms/molecule which means (270 mg gold/ml) and at similar elemental concentration as iodine-based contrast agents., 0.0072 M. Saline could be added to give iso-osmolality. high amounts of gold were used in (GNP) to clarify printed images. Computed Tomography is more sensitive than planar X-ray imaging and there are many studies of contrast agents mark that significant contrast-to-noise X-ray images can get at gold concentrations of 100 mg/ ml [9]. This level is one hundred times lower then a dose of (GNP)at which found so no evidence of toxicity. The use of small amounts of gold clinically would lower the cost and improve the safety margin. The extension of imaging time and significant contrast which provided by (GNP) with the nontoxic effect of intraperitoneal injection open new fields of medical imaging which include enhancement of mammography, renal angiography, aneurysms, a clear plan of stroke and arteriovenous malformations.

Improving the contrast of X-ray imaging might enable noninvasive detection of tiny tumors that are recently missed which lead to better prognoses. Tumor vascularity is correlated with invasiveness [10], so indices of vascularity make non-invasive staging possible. The (GNP) might be beneficial to recognize vulnerable plaque since it is more highly Vascularized (like tumor behavior) than stable plaque [11,12]. With the advantage of faster Computed Tomography machines that lessen motion artifacts, (GNP) -enhanced imaging of coronary arteries, especially those in over weighted patients or those with mural calcifications might prove workable via trans venous injection without the need to catheterization. Contrasting during trans arterial catheterization also, the usage of (GNP) has many advantages and, especially for obese patients where the medical imaging needs extra contrast to provide an X-ray image with accepted information the concentration of gold can be Made five times higher than that of iodine-based contrast agents as well as the absorbance of gold three times higher at 120 keV. the result according to contrast might be greater than 10 fold. This gold retention in tumor site rather than muscles site may be beneficial to enhance tumor detection and may be for therapy because of the improved tumor:non-tumour ratio reached.

## Conclusion

These animal studies demonstrate three important points. The First one is that (GNP) as X-ray contrast agent is very useful and a new gate of X-ray diagnostic may be open by this contrast agent where it offers pharmacokinetic and physical advantages over current contrast agents. It appears as non-toxic contrast agent and improve imaging times and enables higher contrast than iodine based contrast agents. The second point is the intraperitoneal administration is less limited than Intravenous administration and gives more details due to its absorption by the soft tissue. The third point is the usage of rod gold nanoparticles is more accuracy than the usage of spherical gold nanoparticles for intraperitoneal injection.

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