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GOLD NANOPARTICLES: SYNTHESIS AND APPLICATION IN CANCER DIAGNOSIS AND THERAPY

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ABSTRACT

Metal nanoparticles are widely employed in bio-medical applications because of their high thermal stability and low size-to-volume ratio. Due to their simplicity in synthesis, stability, and characterization, low toxicity, and simplicity in detection, gold nanoparticles (AuNPs) are a natural choice for bio-medical applications. The synthesis of gold nanoparticles has been carried out using a variety of chemical techniques over the last few decades. The development of new AuNP synthesis techniques is the main emphasis of this review.

INTRODUCTION

The term "nanotechnology" refers to the development and use of parts that are produced at the nanoscale, or up to 1-100 nm in size.[1] Nanotechnology includes the study of the molecular and submolecular structural characteristics of nano-structures as well as their electrical, optical, and magnetic characteristics. Nanotechnology is now an interdisciplinary topic that unites engineering, biology, chemistry, and physics.[2] This world has entered a new period known as the era of nanotechnology thanks to the use of nanomaterials in many industries such as oil and gas, cosmetics, and nanomedicine.[3,4] Carbon nanotubes, gold nanoparticles, liposomes, and paramagnetic nanostructures are some of the most thoroughly studied nanostructures.[5-8] Gold colloids are presently being used more and more in a variety of disciplines, including chemistry, biology, engineering, and medicine. The biomedical industry has many applications in diagnostics and therapies Given that they are among the most stable, nontoxic, and easily synthesized nanoparticles and display a variety of intriguing features, including assembly of different kinds and the quantum size effect, gold nanoparticles make an excellent research subject.[6] The surface plasmon resonance (SPR),

which spans a broad spectrum from the visible to the infrared area and is controlled by collective oscillation of conducting electrons, determines the optical behavior of gold nanoparticles. The size and form of gold nanoparticles, among other characteristics, have an impact on the spectrum's frequency range. These materials may be made in a repeatable manner utilizing techniques that have been established,[9] and they can then be altered using a huge number of chemical functional groups. Based on the gold nanoconjugates, several novel sensitive and precise tests have been developed. Gold nanoparticles have shown to be a strong contender for use in the delivery of a variety of payloads to the target location.[10,11] These payloads can be anything from very small medication molecules to big macromolecules like proteins, DNA, and RNA. Some therapeutic compounds can be directly conjugated with gold nanoparticles by physical absorption and ionic or covalent bonding without needing to modify a monolayer of gold nanoparticles in order to distribute them.[12] Gold nanoparticles must be functionalized via processes like PEGlyation, peptide and amino acid conjugation,[14,15] or functionalization using oligonucleotides in order to convey additional payloads.[16] Additionally, the release of medicinal substances is a requirement for their effective delivery. Numerous internal (glutathione, pH, and enzymes) and exterior (light, etc.) triggers have been studied for the effective release of glutathione. In recent years, there has been a lot of study on and interest in the field of nanotechnology. The fast advancement of nanotechnology has led to a remarkable expansion in the production and application of nanoparticles (NPs). One of the most significant nanoparticles is gold (AuNPs), and owing to its inert, biocompatible, and particularly low toxicity properties, they have been employed extensively for both medical and non-medical applications as excellent materials.

Gold is inert and universally recognized as biocompatible. Until the recent past, it was only known as the metal. With the arrival of nanotechnology, the discovery of nanoparticles and the exploration of the physicochemical properties of gold make it a supreme material for progress fields.

SYNTHESIS OF GOLD NANOPARTICLES

Two fundamental strategies—the "Top-Down" and "Bottom-Up" approaches—are employed. The top-down strategy entails beginning with bulk material and employing various techniques to break it down into nanoparticles in order to synthesize AuNPs. In contrast, the bottom-up strategy starts with atoms to create nanoparticles. The reduction of Au3+ to Au0 is

a bottom-up way of synthesis, whereas laser ablation, ion sputtering, UV and IR irradiation, and aerosol technology are top-down approaches.

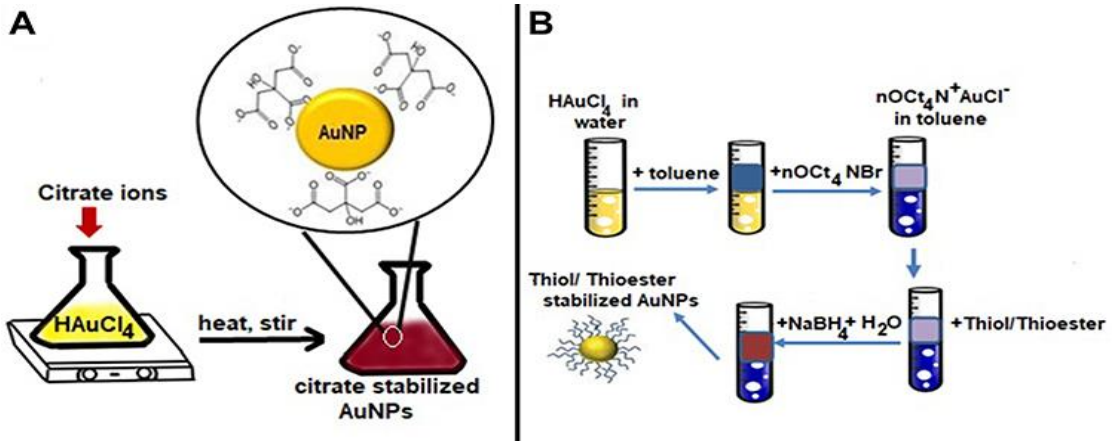
Numerous physiochemical procedures have been used to create nanoparticles, and they have all had a major negative impact on the environment. The lengthy history of medicinal uses of gold nanoparticles makes them the most significant of the metal nanoparticles described above. Gold nanoparticles are the type that has been reported on the most in the literature. Approximately 87,000 articles have been published since 1996. According to **Daruich De Souza et al. (2019)**, copper, silver, iron, and titanium nanoparticles should all be examined independently because they are all well-documented. Numerous distinct biological, physical, and chemical synthesis methods have been established for the production of gold nanoparticles.

There are two primary steps in the formation of AuNPs

1. Using a particular reducing agent, such as citrate, the gold precursor, which is typically an aqueous gold salt solution, is reduced to gold nanoparticles in the first stage.
2. A special capping agent stabilizes the gold nanoparticles in the second stage. The capping agents prevent metallic nanoparticles from clumping together.

1) Turkevich Method

This technique for creating AuNPs was initially described in 1951. It is one of the methods for creating spherical AuNPs that is most often employed. The resulting AuNPs are between one and two nanometers in size.[26] The primary idea behind this method is to use reducing agents such amino acids, ascorbic acid, UV radiation, or citrate to convert gold ions (Au3+) into gold atoms (Au0).[29,30] A variety of capping/stabilizing chemicals are used to stabilize AuNPs. The Turkevich approach initially had a limiting number of applications due to the variety of AuNPs that could be produced using this process. Researchers were able to increase the size of the sample as a result of many breakthroughs in the fundamental technique throughout time. Researchers have been able to broaden the size range of the particles created using this technology because to a number of improvements made to the fundamental technique throughout time. In 1973, it was discovered that specific AuNPs with a size range of 16–147 nm could be generated by changing the ratio of reducing and stabilizing agents.[31-33] Turkevich method is shown in Figure A.



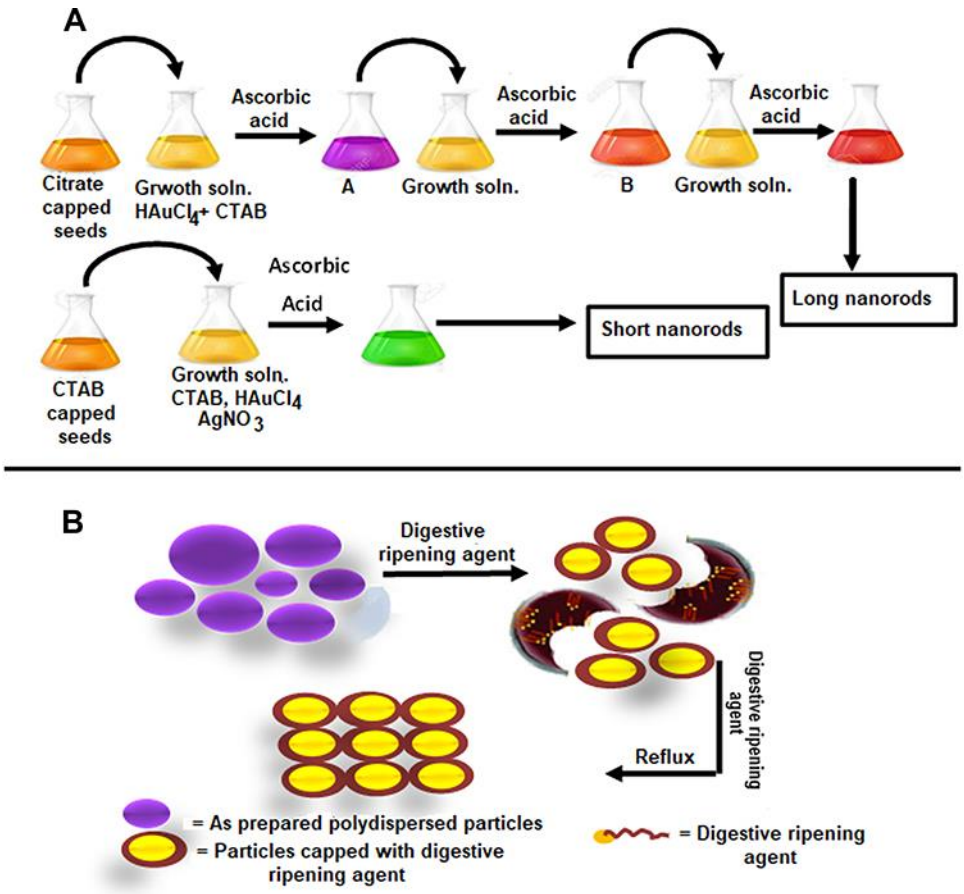
A – Turkevich method, B – Brust method

2) Brust Method

This procedure, which was initially described in 1994, uses a two-phase process and organic solvents to create AuNPs with a size range of 1.5–5.2 nm.[34] The process includes moving gold salt from its aqueous solution to an organic solvent (like toluene) using a phase transfer agent like tetraoctylammonium bromide. The gold is subsequently reduced using an alkanethiol and a reducing agent, such as sodium borohydride. The stabilization of AuNPs is carried out by the alkanethiol.[35] This process causes the hue to shift from orange to brown.[34,36] The schematic representation of the key phases in the Brust approach is shown in Figure B.

3) Seed Mediated Growth

The two processes mentioned above can only produce spherical AuNPs, although they may also be formed into many shapes and geometries, including rods.[37,38] The process of seed-mediated development is the one that is most frequently utilized to create rod-shaped AuNPs. The underlying idea behind this procedure calls for first manufacturing seed particles by reducing gold salts. Reducing agents like NaBH4 are used during this process. The seed particles are then transferred to a metal salt and a mild reducing agent, such as ascorbic acid, to stop further nucleation and hasten the synthesis of rod-shaped AuNPs. The concentration of reducing agents and seeds determines the shape and geometry of gold nanoparticles.



4) Digestive ripening

In the presence of too many ligands (digestive ripening agents), digestive ripening is thought to be a practical way to create monodispersed gold nanoparticles. According to Figure 3B, the fundamental procedure is heating a colloidal solution at high temperatures (about 138oC) for two minutes and then heating it at 110oC for five hours. The primary factor affecting the size distribution of the gold colloids is temperature.

CHARACTERIZATION OF GOLD NANOPARTICLES

1) UV-Vis (ultraviolet-visible) Spectroscopy

The unique optical property of gold nanoparticles is known as localized surface plasmon resonance (LSPR), which is the collective oscillation of electrons in the conduction band of gold nanoparticles in resonance with a particular wavelength of incoming light. UV-Vis spectroscopy measures the strong absorbance band that occurs from the LSPR of gold nanoparticles in the visible range (500–600 nm). The LSPR spectrum is influenced by the gold nanoparticles' size (Figure 1) and shape (Figure 2). When considering unevenly shaped particles like gold nanourchins, the absorbance spectrum changes dramatically into the far-

red area of the spectrum in comparison to a spherical particle of the same diameter. The peak absorbance wavelength rises with particle diameter.

The sample's peak optical density (OD), also known as absorbance, has a linear relationship with the amount of nanoparticles in solution. Please refer to table 1 below to connect the OD value of each size of particle with its concentration (particles/ml). For nanoparticles between 5 and 100 nm, an OD value of 1 (with a 1 cm pathlength) is applicable.

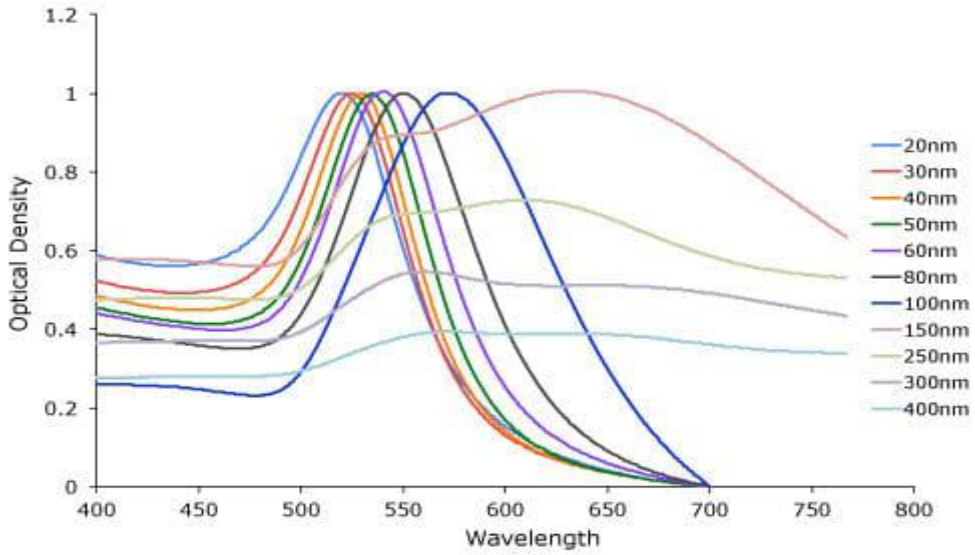


Figure 1: Gold nanoparticle size dependant surface plasmon resonance. Note the red-shift of the absorption maximum as the gold nanoparticle size increases.

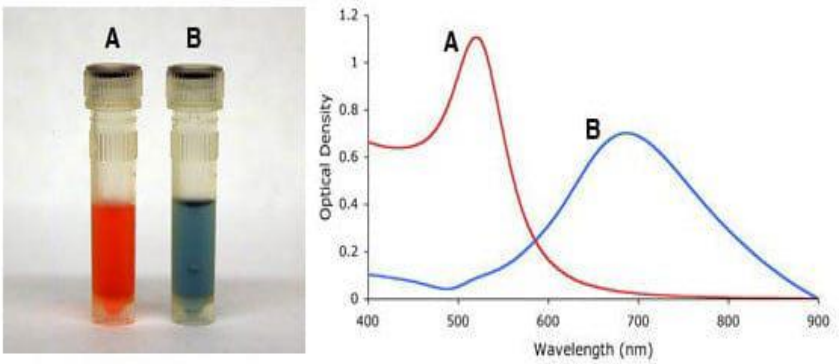


Figure 2: Gold nanoparticles shape dependent surface plasmon resonance as indicated by the visual appearance and UV-VIS spectra of spherical (A), and urchin-shaped (B) gold nanoparticles ("spiky gold").

2) Dynamic Light Scattering

(DLS) is an analytical method for determining a submicron particle's size and size distribution. In order to determine the size of the particles and determine their Brownian motion velocity, a laser beam is used to illuminate a suspension of particles. The fluctuation of scattered light is then tracked and studied. DLS quantifies a particle's hydrodynamic size, which takes into account the particle's solvent layer and surface coating in addition to the physical size of the nanoparticle core.

Consequently, the hydrodynamic size of gold nanoparticles is increased upon conjugation of molecules such as PEG, proteins, or oligonucleotides to their surface. Therefore, this method offers an additional tool for assessing surface alterations. A PEG layer's 20 nm gold nanoparticle binding is seen in the figure.

DLS may also be used to measure the aggregation of gold nanoparticles. Although DLS measures non-aggregated monodispersed gold nanoparticles as a single size population, particle aggregation can result in a widening of the peak, an increase in hydrodynamic size, or even numerous populations.

When it comes to measuring the size of particles, assessing surface modification, tracking the stability of gold nanoparticles over time, and detecting approaches for bio-assays, DLS measurement of gold nanoparticles is a particularly sensitive technique.

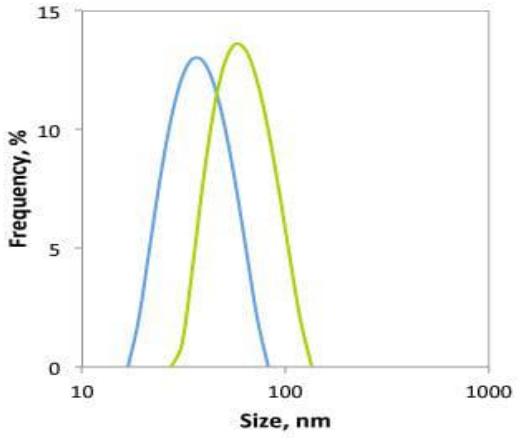
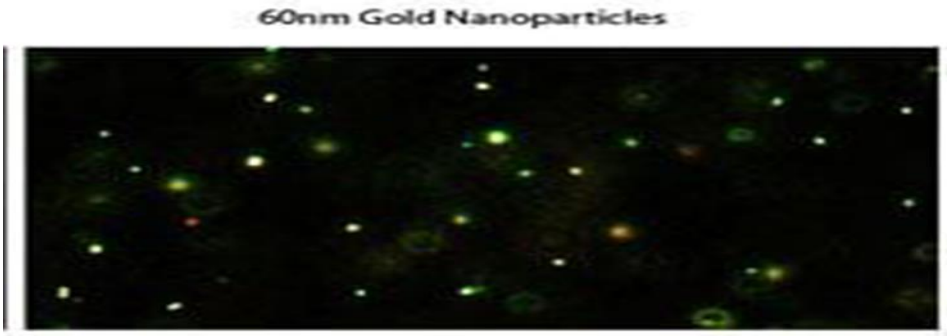


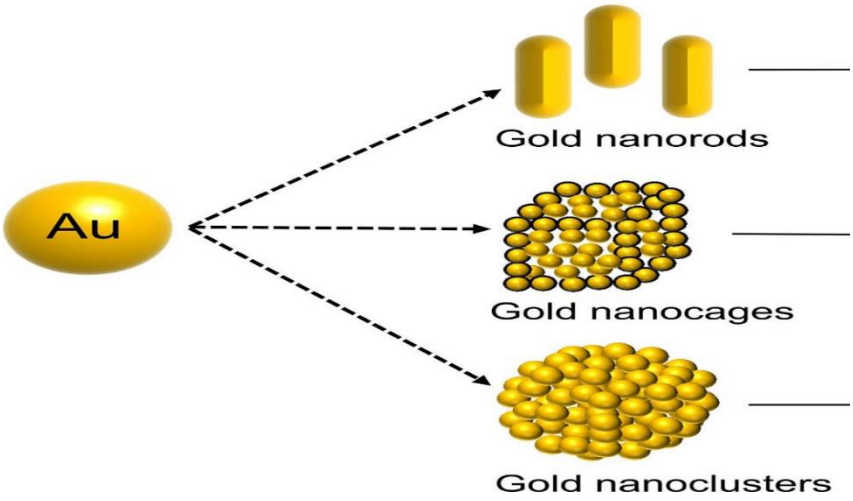
Figure: Size histogram obtained by dynamic light scattering measurement of 20 nm gold nanoparticles before (blue) and after (green) surface functionalization with a 3kDa PEG-thiol. The hydrodynamic size increased from 30 nm to 48 nm through the addition of a PEG-layer.

3) Microscopic Imaging of Gold Nanoparticles

Dark field microscopy is another significant microscopic method for seeing gold nanoparticles. Gold nanoparticles may be seen under a dark field microscope as brilliant spots due to intense surface plasmon resonance light scattering. The wavelength of the peak SPR determines the color exhibited. Peak SPR and scattering of gold nanoparticles occur in the 500 nm range, as demonstrated by the dark field microscopy images in Figure.



TYPES OF GOLD NANOPARTICLES



1) Nanorods

According to research, gold nanorods modified with the RLT polypeptide, which binds to the low-density lipoprotein binding domain, have a fairly noticeable inhibitory impact on gastric cancer cells. Additionally, they showed improved biosafety in vivo as compared to the free medication doxorubicin and considerable anti-tumor activity in the treatment of malignancies.[32] This gold nanorod can promote mitochondrial malfunction, lessen the capacity of the mitochondrial membrane to activate cell apoptosis, increase the formation of singlet oxygen, and decrease the ability of the gold nanorod to bind serum proteins.[33]

2) Nanocages

One variety of gold nanoparticles is called a gold nanocage, which has a hollow cage-like structure. They are more drug-loaded than the other two gold nanoparticles because to their high specific surface area, excellent surface modifying characteristics, and high specific surface area.[36,37] The combination of rubescensine A, hyaluronic acid (HA), anti-GPC-1 antibody, and gold nanocages inhibited pancreatic cancer. Additionally, gold nanocages have the capacity to image in several modes, including magnetic resonance imaging (MRI) and near-infrared fluorescence (NIRF), which can identify pancreatic cancer at an early stage.[38] A compound was created by combining the PDL1 antibody, a TGF-inhibitor, and gold nanocages, which can target colon cancer cells with precision and gather in tumors.

3) Nanoclusters

When compared to gold nanorods and nanoclusters, gold nanoclusters have significantly lower cytotoxicity and superior red fluorescence properties, which enable them to successfully avoid autofluorescence background in vivo.[41,42] Gold nanoclusters are extremely small particles made up of a few to a few hundred gold atoms.[41] and they are composed of several to a few hundred gold atoms. Gold nanoclusters coated with folic acid linked silica have also been created, and they efficiently target stomach cancer cells and have good red fluorescence optical qualities. They can be employed for optical and CT dual-mode imaging of gastric cancer and have a lot of potential applications for in vivo early detection of gastric cancer.[43]

Application of Gold Nanoparticles in Diagnosis and Therapy of Cancer

The GNPs have low in vivo toxicity, are nonimmunogenic, and are stable. Additionally, they can accumulate in tumor areas as a result of the EPR effect, making them appealing for imaging diagnosis. The use of conventional CT contrast agents is constrained by their small molecular size, short circulation duration, and adverse side effects as nausea and itchiness. Due to their high x-ray attenuation coefficient and biocompatibility, GNPs are a potential CT contrast agent). By targeting mouse colon cancer cells and serving as a CT contrast agent, a monoclonal antibody against HSP70 conjugated to GNPs demonstrated outstanding imaging capabilities in spectral CT and excellent sensitivity for the identification of even single cells.

Particle name	Nanoparticle Size	Detection
AuNCs@SiO2-FA	~58 nm	Gastric cancer
CG-GNPs	20nm	Head and neck squamous cell carcinoma
cmHsp70-AuNPs	54 ± 11 nm	Colorectal cancer
PPHAuNCs-TNCs	30nm	Pancreatic ductal adenocarcinoma
Ac-PE-AuNPs	95.4 ± 2.4 nm	Hepatoma carcinoma
Fe3O4@Au@β-CD	71.40nm	Gastric cancer
GoldMag	~50nm	Pancreatic cancer

GNPs now have a significant impact on the management of gastrointestinal malignancies. A novel cancer therapy called photothermal therapy (PTT) can target tumor tissue and heat it while sparing healthy tissues from harm. The plasmonic nanoparticles are NIR-irradiated and then transported to the tumor cells or tissue, where the absorbed light is transformed into heat, irreparably harming the neighboring diseased tissues. Many different nanoparticles are employed in PTT, but GNPs in particular can passively accumulate in tumor tissue. Additionally, their structural makeup may be changed to best absorb NIR light (650–1350 nm), which has become a significant therapeutic platform for photothermal treatment. With the use of photosensitizing medications and laser activation, photodynamic therapy (PDT) is a revolutionary approach for treating neoplastic disorders. When the photosensitizers are applied to the tumor cells or tissues and exposed to a particular laser wavelength, a highly reactive oxygen species) is created that slows the development of the tumor). Indocyanine green (ICG), a tricarbocyanine dye that has been given FDA approval as a possible near-infrared photosensitizer for clinical imaging and diagnostics, is the most widely used photosensitizer. However, due to its low stability and quick blood elimination, ICG cannot be used for photodynamic treatment or fluorescence imaging). Therefore, it is a good idea to create a new cancer therapy that combines PTT with PDT to treat gastrointestinal cancer.. In order to target the endoplasmic reticulum (ER), hollow gold nanospheres (HAuNS) were first coated with indocyanine green (ICG) and then modified with fal polypeptide (FAL). This created a PTT/PDT composite nanosystem. When exposed to NIR radiation at 808 nm, there was a simultaneous rise in temperature and ROS production, which caused ER stress and boosted the immunological response. ICG molecules were conjugated to gold nanospheres (HAuNS) using a linker made of branched polyethylene glycol (PEI), which has a molecular

weight of 10 kDa. By combining PTT with PDT treatment, this innovative nanosystem can prevent tumor development and metastasis.[44]

ADVANTAGES AND DISADVANTAGES OF GOLD NANOPARTICLES

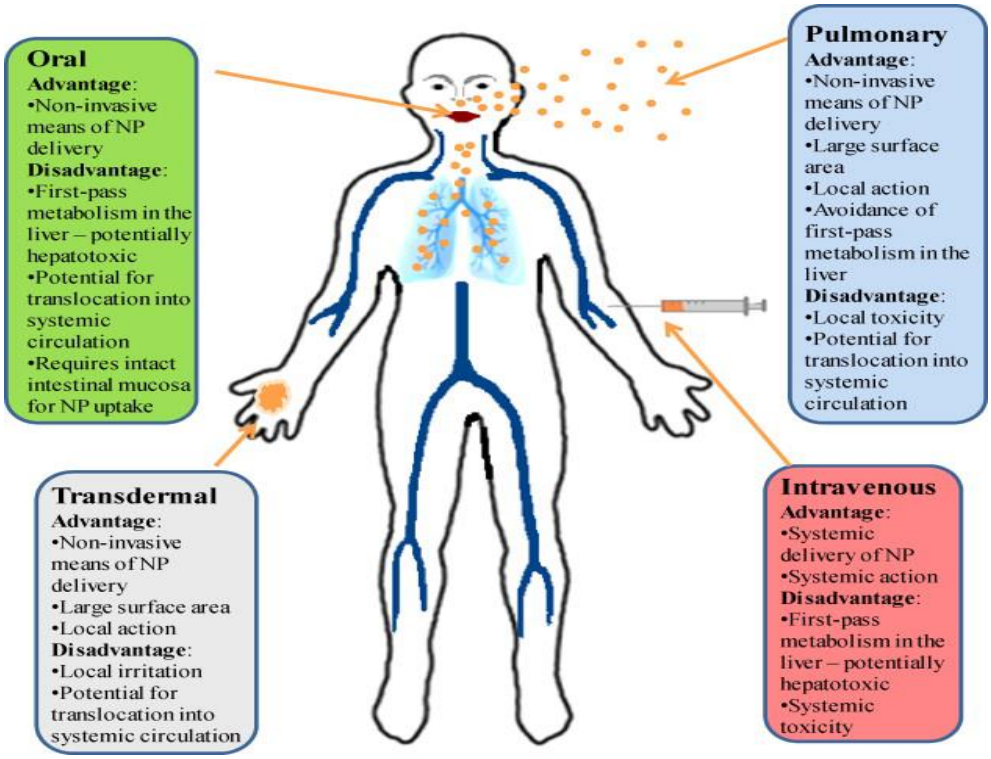
ADVANTAGES

1. Particle size can be manupulated easily for active and passive drug targeting
2. Drug can be incorporated without any chemical reaction
3. Site specific drug targeting can be done by attaching targeting ligand to surface of gold nanoparticles
4. Administration through various routes like oral, nasal, parenteral etc
5. Increase Bioavailability

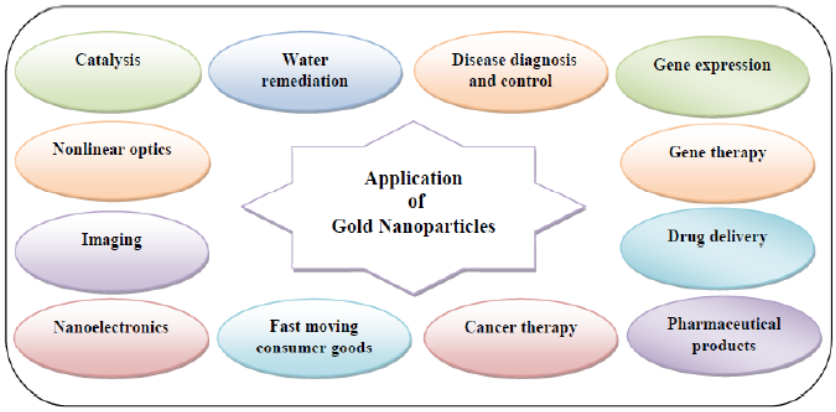
DISADVANTAGES

1. May alter physical properties and cause particle-particle aggregation
2. Very reactive in cellular environment
3. Small particle size responsible for limited drug loading
4. More expensive
5. Short shelf live

ROUTES OF ADMINISTRATION FOR GOLD NANOPARTICLES



APPLICATIONS OF GOLD NANOPARTICLES



FORMULATIONS OF GOLD NANOPARTICLES

CONCLUSION

In this review article, we have discussed various methods for synthesis of gold nanoparticles types of gold nanoparticles and application of gold nanoparticles in cancer diagnosis and therapy. Future research should focus on creating a unique gold nano drug delivery system that can perfectly carry and discharge payload at the target site, even if each of these drug release techniques has its own limits. In conclusion, gold nanoparticles present a viable approach; nevertheless, further research on the effectiveness of in vivo delivery and clinical trials are needed. Additionally, the production procedure is quick and easy. Gold nanoparticles are used to identify and treat gastrointestinal cancer. Thus, GNPs are a potential imaging, diagnostic, and therapeutic tool for gastrointestinal malignancies.

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