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GOLD NANO PARTICLES: A NOVEL DRUG DELIVERY

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ABSTRACT

In every field of life, nanotechnology has an impact. Researchers expend their interests on gold nanoparticles synthesis as they provide superior properties for various types of applications. Different physical and chemical methods have synthesized conventionally nanoparticles that have a negative impact on the environment. Due to their unique properties, small size and high area-to-volume ratio, gold nanoparticles show special advantages in this field among nanoparticles. Because of their inert nature, stability, high dispersity, non-cytotoxicity and biocompatibility, these particles have been widely used in various biomedical applications and drug delivery systems. This paper shows the comparison and survey of all the methods.

Keywords: Gold nanoparticles, Nanotechnology, drug delivery, biomedical applications.

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INTRODUCTION

In recent years, nanotechnology has become one of Physics, Chemistry, Engineering and Biology's most important and exciting front lines. It shows great promise to give us many breakthroughs that in a wide range of applications will change the direction of technological advances. The nanotechnology research area is interdisciplinary, covering a wide range of topics ranging from nanoparticles catalyst chemistry to quantum dot laser physics. As a result, researchers need to go beyond their expertise in any particular area to appreciate the wider implications of nanotechnology and learn how to contribute to this exciting new field. Particles of 1-100 nm size are called nanoparticles, whether dispersed in gaseous, liquid, or solid media. Because NPs are larger than individual atoms and molecules but smaller than bulk solids, materials in the regime of nanometres size show an intermediate behaviour between that of a macroscopic solid and that of an atomic or molecular system.

Nanotechnology is based on the recognition that particles below the size of 100 nm convey new properties and behaviour to nanostructures built from them. The electronic structure, conductivity, reactivity, temperature melting and mechanical properties were all observed to change when particles are smaller than a critical size. The behaviour's dependence on the particle sizes can enable one to develop their properties. The properties of nanometre-dimensional materials differ significantly from those of atoms and bulk materials. There are three major factors responsible for these differences: the high ratio of surface to volume, the effect of quantum size and the interactions of electrostatics.

All nanoparticles irrespective of their chemical constituents have extremely high surface-to-volume ratios. Thus, the nature of the NP surface dominates many of the physical properties of nanoparticles such as solubility and stability. The appearance of quantization effects due to the containment of electrons movement is one of the direct effects of reducing the size of materials to the nanometres range. Depending on the size of the structure, this results in discrete energy levels. Following these lines, it is possible to create artificial structures with properties other than the corresponding bulk materials. Dimensional control as well as structural composition makes it possible to customize material properties for specific applications¹.

According to the American Society for Testing and Materials (ASTM), nanoparticles are particles of two or more dimensions with a size range of 1 to 100 nm².

Due to their large reactive and exposed surface area and quantum size effect due to specific electronic structures, these particles have special and enhanced physical and chemical properties

compared to their bulk materials. These particles were widely used in many fields, including electronics, photochemistry, biomedicine and chemistry³.

Much attention has recently been given to controlling the shape and size of metal nanostructures because their shape and size influences all the magnetic, catalytic, electrical and optical properties of metal nanostructures. Nanoparticles have extensive applications in the field of biomedicine, such as pharmaceutical delivery, diagnostic approaches and therapeutic applications, because nanoparticles have very small particles, they can be used for targeted drug delivery and metallic nanoparticles respond resonantly to the time-varying magnetic field in order to transfer sufficient toxic thermal energy⁴.

Nanoparticles cover a wide area of interest including electronics, medicine, food industry, applications for the environment and cosmetics. Moreover, due to the metallic properties, these metal nanoparticles have a photoelectric effect that neutralizes the photo bleaching concerns associated with conventional fluorescent colours. The surface modification of the nanomaterials has a strong effect on the interaction between these nanomaterials and cells, as well as helping to convert toxic nanomaterials into less toxic or less toxic nanomaterials into more toxic nanomaterials⁵.

Nanoparticles great potential is due to the unique properties of elements when their size is reduced to the level of Nano-meter. Overall, particle properties above the Nano-meter size are not significantly different from their bulk counterparts. However, their physical and chemical properties can drastically change if particles are reduced to their Nano-level. Changes in these properties are highly influenced by the shape, size and nature of their surroundings⁶.

Because of their increased biocompatibility, stability and oxidation resistance, AuNPs are considered one of the most convenient carrier systems. Colloidal gold is therefore applicable in different fields of medical research, including biosensing and bio detection, catalysis and bioelectronics, drug delivery carriers and macromolecular carriers, bioimaging and photo hyperthermia⁷.

Collectively, one can conclude that, during the manufacturing process of Nanosystems with potential applications in controlled and targeted drug therapy, the gold nanoparticle surface charge plays a critical role. Taking into account these unique properties of AuNPs, but also the current challenges to personalized medical care, gold nanoparticles have the attractive potential for engineering novel nanostructured tools for selective tumour targeting and imaging, thus highlighting their tremendous potential in unconventional cancer diagnosis and treatment⁸.

AuNPs surface load, estimated in terms of zeta potential, facilitates their physicochemical stability and further implementation in the process and bioaccumulation of cells. As many previous studies have shown, the level of toxicity assigned to AuNPs is heavily dependent on the particle surface load, so the positively charged gold nanoparticles cause cell death at lower concentrations, whereas the neutrally charged particles determine cell death at significantly higher concentrations⁹.

Metal nanoparticles, specifically gold nanoparticles, are widely used in biotechnology and biomedicine because they have a large bioconjugation with molecular samples and many optical properties that are mainly concerned with localized plasmon resonance¹⁰.

Different chemical and physical methods have been adapted for the synthesis of expensive nanoparticles and harmful to the environment are the chemicals used. The emerging field of current era research is to overcome these problems of green synthesis. Inorganic nanoparticles are used in molecular imaging as contrasting agents such as positron emission tomography (PET), magnetic resonance imaging (MRI), ultrasound and optical imaging, computed tomography (CT)¹¹.

Nanoparticles were used to enhance the drug delivery system's selectivity and efficiency because they act as drug release mediators. Nanoparticles are extremely small in size and have a high surface area, so their surfaces are available for further modification with hydrophobic, hydrophilic, cationic, anionic or any neutral features in the surrounding environment, so they have a lot of application in biological sciences. Nanoparticle-based drug delivery systems have proven to be a great way to target malignant brain tumours where conventional therapy is less effective. The unique property of nanoparticles to accumulate and interact with tumour cells is enhanced permeability and retention (EPR)¹².

I. GOLD NANO PARTICLES

Gold nanoparticles properties differ from their bulk form because bulk gold is yellow solid and inert in nature, while gold nanoparticles are red wine solution and are reported to be antioxidant. Inter particle interactions and assembly of networks of gold nanoparticles play a key role in determining the properties of these nanoparticles. Gold nanoparticles have different sizes ranging from 1 nm to 8 μ m and have different shapes such as spherical, suboctahedral, octahedral, decahedral, multiple twined, multiple twined, irregular shape, tetrahedral, nanotriangle, Nano prism, hexagonal platelets and nanorods (Figure 1). Triangular shaped nanoparticles show attractive optical properties compared to spherical shaped nanoparticles among all of these shapes.

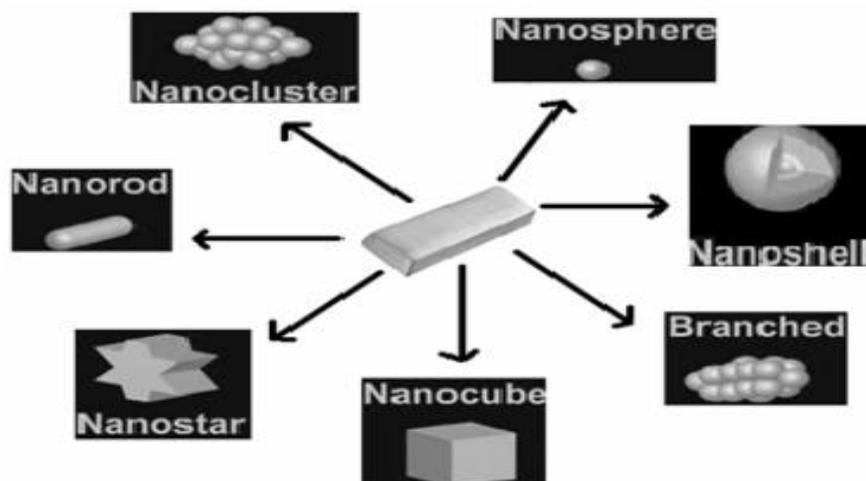


Figure 1: Various shapes of gold nanoparticles

II. METHODS FOR SYNTHESIS OF GOLD PARTICLES

Different methods for the synthesis of gold nanoparticles have been developed and these methods follow the same rules as other particle preparation methods. General methods for gold nanoparticles synthesis include chemical, physical, and biological methods, terkovich method, seeding growth method, electrochemical method, green method described below:

1. Physical Method:

The π -irradiation technique is one approach to Au / NPs synthesis with a uniform size of 5-40 nm and high purity using polysaccharide alginate as a stabilizer¹³. By reducing agents such as citric acid and a binding agent such as cetyltrimethylammonium bromide (CTAB), the microwave irradiation technique was used to prepare Au / NPs. In addition, Au / NPs are prepared with heat or photochemical reduction and HAuCl₄ reduction with citrate, tartrate and malate¹⁴.

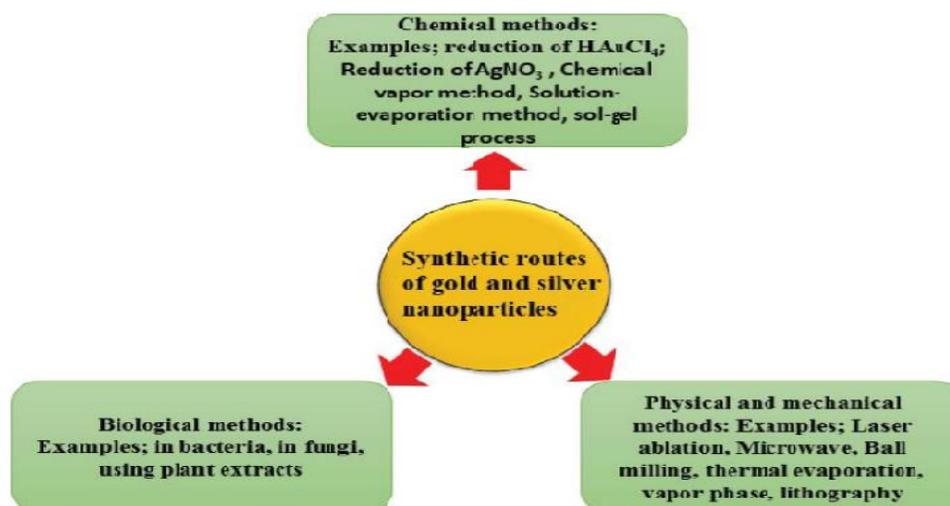


Figure 2. Different methods of synthesis of nanoparticles

For the synthesis of gold-polyethylene glycol nanoparticles by polymerization reactions of size 10-50 nm, a common method of photochemical reduction has been recorded. In addition, the radical formation of glycol diacrylate coated with polyethylene glycol by UV reaction reduces gold salt¹⁵.

2. Chemical Method:

In general, the chemical reduction method used to prepare AuNPs includes two main parts: a) Reduction of agents such as borohydrides, formaldehyde, aminoborans, hydrazine, hydroxylamine, polyols, citric and oxalic acids, hydrogen peroxide, carbon monoxide, sugars, sulfide testers, hydrogen, acetylene and electronic reduction agents including electron-rich transition metal sandwich complexes; b) Stabilization with agents such as trisodium citrate dihydrate, sulfur ligands (including thiolates), phosphorus ligands, oxygen-based ligands, nitrogen-based ligands (including heterocyclic compounds), dendrimers, polymers and surfactants (including cetyltrimethylammonium bromide). In order to avoid particle aggregation, some sort of stabilizing agent is usually added¹⁶.

Gimenez et al proposed a method for synthesizing gold nanoparticles supported by an insoluble thiolated chitosan derivative by reducing HAuCl₄ by means of thiolated chitosan (QTDT) as a reduction and coupling agent for gold nanoparticles in order to use the synthesized QT / Aunano as a good catalyst to reduce methylene blue

Dendrimers / Au nanoparticles were prepared using the reduction method. These particles were synthesized by sodium borohydride reduction of aqueous HAuCl₄ solution and dilution of dendrimers¹⁷.

Highly stable gold nanoparticles of size 7.8 + 1.7 nm were synthesized by sodium borohydride reduction of HAuCl₄ as a reduction agent. Bovine serum albumin was used as a capping agent in this method and gold-capped protein nanoparticles were reported¹⁸.

Hot injection technique is reported using various surfactants such as oleylamine, 1-octadecanethiol, poly (N-vinylpyrrolidone) and AgNO₃ in 1,5-pentanediol to stabilize the colloidal solution to synthesize gold nanoparticles. In this method, gold nanoparticles were synthesized in the presence of a stabilizing agent by the chemical reduction of gold salt in organic solvent¹⁹.

3. Turkevich method:

One of the most popular techniques for AuNPs synthesis is based on reducing HAuCl₄ by citrate in water, which Turkevich designed first in 1951. The HAuCl₄ solution is boiled in this method and the trisodium citrate dihydrate is then quickly added under vigorous stirring to the boiling solution. The solution's color changes from light yellow to wine red after a few minutes. This is the

result of the method in AuNPs with a diameter of about 20 nm. Citrate ions play a double role in this technique, as they both stabilize and reduce agents²⁰.

Figure 1 shows the schematic route for AuNPs synthesis using the Turkevich method.

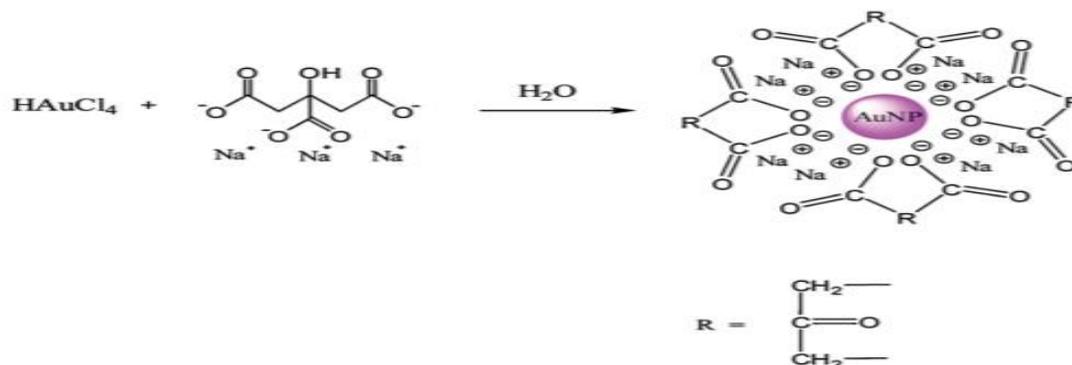


Figure 3: AuNP synthesis using the Turkevich method

In 1973, Frens modified the Turkevich method to obtain AuNPs with diameters ranging from 15 to 150 nm by controlling the reduction agent / stabilizing agent ratio (trisodium citrate / gold). Several research groups have further modified the Turkevich-Frens method²¹.

Puntes et al. reported that adding reagents in the reverse sequence (adding HAuCl₄ to a boiling sodium citrate solution) leads to the production of small-sized AuNPs and a narrow size distribution²².

Recently, a theoretical model and experimental results indicated the important role of sodium citrate on the pH of the solution and its role in controlling the size of the nanoparticle²⁰.

4. Electrochemical Method:

In 1994, Reetz et al. studied the electrochemical production of nanoparticles (Reetz and Helbig 1994, Reetz et al. 1995). Their studies have shown that the size-selective nano scale of transition metal particles can be set electrochemically using tetra alkyl ammonium salts as metal cluster stabilizers in a non-aqueous medium²².

Use the electrochemical synthesis technique to prepare gold nanoparticles on the surface of multi-walled carbon nanotubes with glassy carbon electrodes²³.

Freeman et al. 1995, Chen and Yang 2002, Haruta and Dat é 2001, Kuge et al. 2000, Kamat et al. 1998 proposed method, Due to its modest equipment, low cost, lower processing temperature, high quality and easy control of yield, the electrochemical process was verified to be superior to other methods of nanoparticles production.

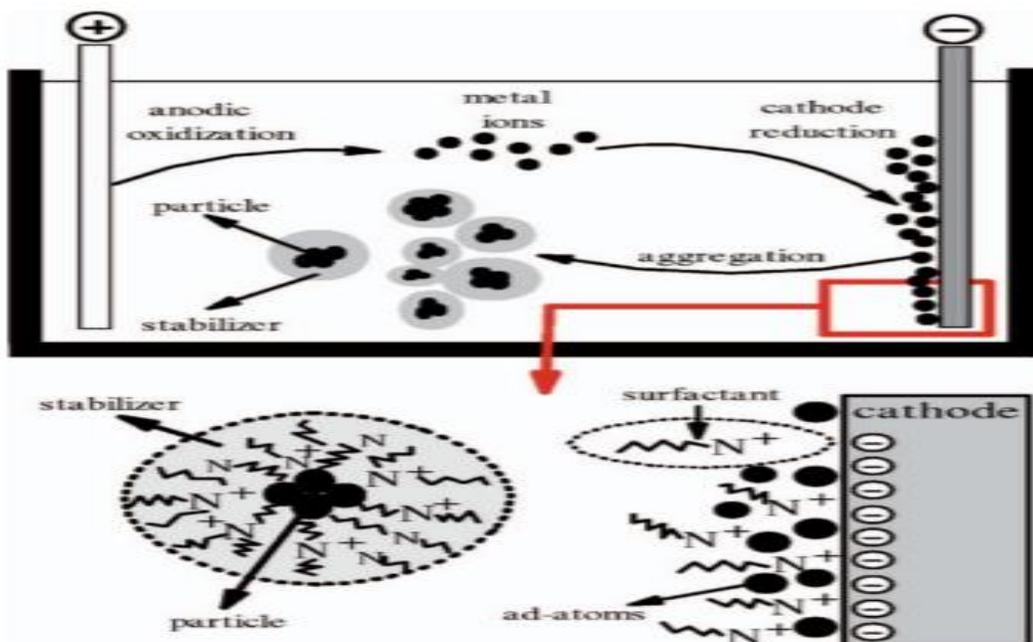


Figure 4. The electrochemical system for synthesizing gold nanoparticles.

The gold nanoparticles were electrochemically prepared using a simple two-electrode cell, with anode oxidation and cathode reduction. Figure 4 shows the electrochemical apparatus schematically.

5. Seeding growth method:

Another method also reported for the synthesis of gold nanoparticles is the method of seed growth. Gold nanoparticles of 5-40 nm diameter and a narrow size distribution have been synthesized according to the seed growth process. The particle size can be controlled by the variable ratio of seed to metal salt and can therefore be prepared in any size of 5-40 nm²⁰.

Advantage of these method of being a simple, fast and low-cost process; while trisodium citrate was used in the seeding stage as a source of OH⁻ ions, sodium borohydrate (NaBH₄) was used as a reduction agent which is shown in Figure 5.

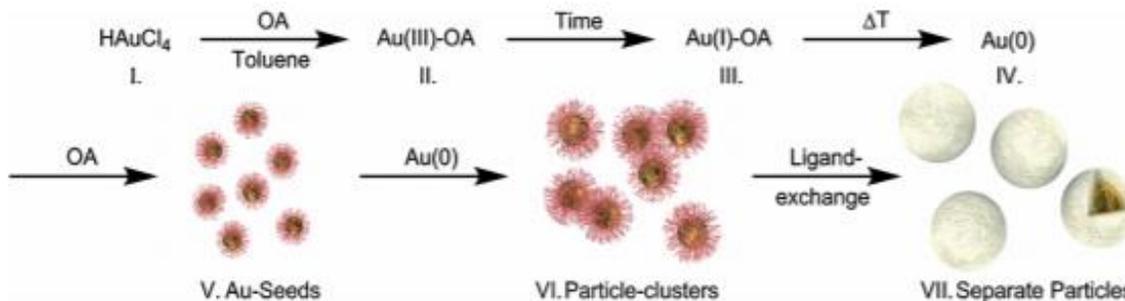


Figure 5. Seeding Growth Approach to Gold Nanoparticles

6. Biological method:

Because of their availability, low cost, eco-friendliness and non-toxic nature, the use of plants for the synthesis of nanoparticles has recently gained importance. The biosynthesis of AuNPs using plants like *Azadirachta indica*, *Medicago sativa*, *Aloe vera*, *Cinnamomum camphora*, *Pelargonium graveolens* (Shankar et al. 2004), *Coriandrum sativum*, *Terminalia catappa*, and lemongrass has been reported in recent years.

While chemical methods are the most common approach to metallic nanoparticles synthesis, their applications are limited by the use of expensive and toxic reagents as reducing and stabilizing agents. These nanoparticles can also have harmful effects in biomedical applications²⁴. Therefore, eco-friendly and cost-effective procedures for the synthesis of nanoparticles that do not use any toxic chemicals are becoming increasingly necessary. Biological nanoparticles synthesis has been at the center of attention in recent years as a green and environmentally friendly method. In biological methods, microorganisms, enzymes and plant or plant extracts synthesize nanoparticles²⁵.

Many papers reported AuNP synthesis using plant extracts such as *Memecylon umbellatum*, *Macrotyloma uniflorum*, *Brevibacterium casei*, *Citrus limon*, *Citrus reticulata* and *Citrus sinensis*, *Piper pedicellatum*, *Terminalia chebula*, *Memecylon edule*, *Nyctanthes*.

7. Green method:

A new method of green chemistry for the preparation of gold nanoparticles was reported in which gold nanoparticles were formed by natural chitosan in aqueous NaCl solution from the bulk gold substratum without using any external stabilizer and reducing agent²⁶.

By adopting a method of sunlight irradiation, gold nanoparticles were successfully synthesized and modified with folic acid and capped with 6-mercaptopurine. Solar energy has been used in this method to reduce gold salt²⁷.

Synthesis routes for green chemistry are environmentally friendly and non-toxic. The use of natural biomaterial egg shell membrane (ESM) has been reported as an easy green biosynthesis method for the preparation of 25 + 7 nm gold nanoparticles. In this method, ESM was immersed in a watery H₂AuCl₄ solution without any reductant²⁸.

A further green synthetic route also synthesizes gold nanoparticles of the size 15-80 nm. In this method, the use of citrus fruit juice extracts reduced H₂AuCl₄²⁹.

Another green synthetic approach was developed with the use of high-power ultrasounds and sodium dehydrate to synthesize gold nanoparticles of size 5-17 nm³⁰.

IV.APPLICATION OF GOLD NANOPARTICLES

Figure 6 illustrates the various pharmaceutical applications of nanoparticles. The wide applicability of gold nanoparticles is due to the Nanoparticles novel properties, which contribute to excellent catalytic applications, good biocompatibility, large surface area, and conductivity . Bio-sensing applications are widely used when the nanoparticles combined with biomolecules and used in combination with Au / NPs and AuNPs / MPA (mercaptropionic acid) used in the manufacture of biosensors showing a wide linear range between 0.25 mM and 0.025 mM glucose concentration.



Figure 6. Application of gold nanoparticles.

1.Application in biomedical:

Nanoparticles are used as biolabels in biomedical applications. Specific recognition, covalent coupling, physical adsorption and electrostatic binding have been reported using various methods to provide hybrid molecules. For example, gold nanoparticles are used in vivo gene therapy, proteins, nucleic acid delivery and targeting. Fig.7 shows the application of gold nanoparticles in biomedical²⁰.

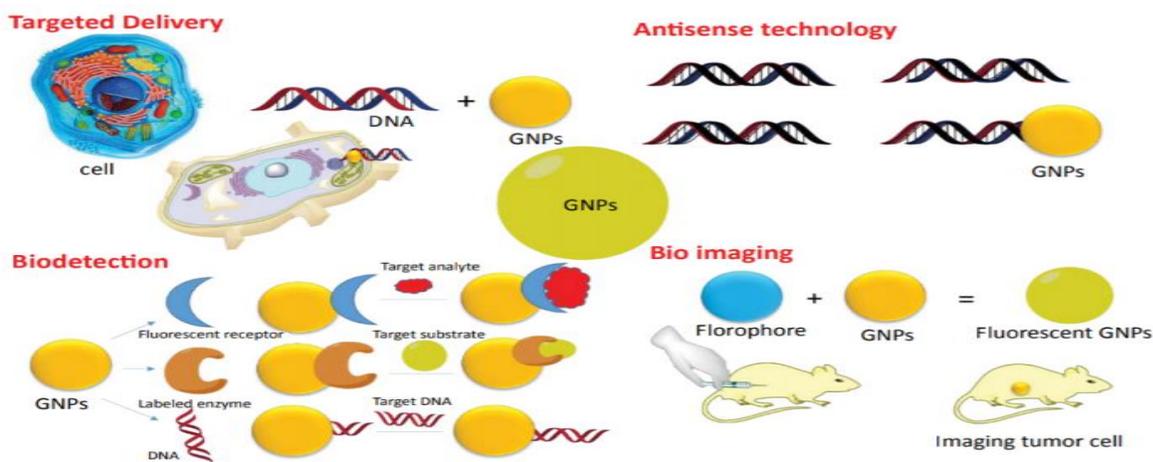


Figure 7. The potential application of Gold nanoparticles in the biomedical field.

2. Application of Gold nanoparticles in Chemotherapy:

The use of colloidal gold in therapeutic treatments, often for cancer or arthritis, is gold nanoparticles in chemotherapy and radiotherapy. The technology of gold nanoparticles shows promise to advance cancer treatments. Some of the properties of gold nanoparticles, such as small size, non-toxicity and non-immunogenicity, make these molecules useful for the targeted delivery of drugs. With tumor - targeting delivery vectors becoming smaller, it becomes more likely to be able to bypass the body's natural barriers and obstacles. In order to increase the specificity and likelihood of drug delivery, tumor - specific ligands can be grafted onto the particles together with the chemotherapeutic drug molecules to allow these molecules to circulate throughout the tumor without redistribution into the body.

The nanoparticles flow in endocytosis and are diffused through the lipid bilayer of the cell membrane. To bind specifically to cancer cells, nanoparticles combined with antibodies against exclusive cancer cell surface receptors are used. The nanoparticles that are functionalized are used for targeted cell entry. Phthalocyanin - stabilized nanoparticles for photodynamic therapy have been shown to be a potential delivery vehicle²⁴.

Treatments:

- Photothermal cancer therapy
- Radiofrequency therapy
- Angiogenesis therapy
- Anti-bacterial therapy
- Drug vectorization

Photothermal cancer therapy:

A direct method of accessing and destroying tumour cells can be accomplished by photothermal cancer therapy or photodynamic therapy (PDT). This procedure is known to treat small tumours that are difficult to access and prevent the inconvenience (adverse effects) of conventional methods, including unnecessary destruction of healthy tissues. By exposure to light, the cells are destroyed, rupturing membranes causing digestive enzyme release. AuNPs have high cross-sections of absorption that require only minimal energy input from irradiation. It has been shown that human breast carcinoma cells infused with in vitro metal nanoparticles have increased morbidity with near-infrared exposure (NIR).

The same effect was experienced by short-term in vivo exposure (4–6 minutes) to NIR. Hirsch et al observed that extreme tumour heating would cause irreversible tissue damage including coagulation, cell shrinkage, and nuclear stress loss. The results of their mice's in vivo nanoshell

therapy revealed tumour penetration ~5 mm. The metal particles were tuned to high absorption and dispersion, resulting in an effective conversion of light into heat covering a wide area.

There are various advances in biotechnology for drug delivery *in vivo*. The AuNPs were conjugated by polyethylene glycol, a process known as PEGylation, to effectively target malignant cells. This masks the immune system's foreign particles so that it reaches its destination and increases the system's circulation time. Antibody conjugation lines the nanoparticles' surface with cell markers to limit their spread to malignant cells only.

Radiofrequency therapy:

Radiography procedures involve the diagnosis of cancer cells through the image acquisition process. These techniques rely on x-ray absorption in the exposed tissue to improve image quality. A contrast agent is injected into the targeted cancer tissue in certain radiological procedures such as radiofrequency therapy, resulting in increased x-ray attenuation²⁸.

Treatment with radiofrequency therapy involves the destruction of tumour tissue cells by radiofrequency diathermy through the differential heating of cancer tissue. This differential heating results from the supply of blood in the body that carries the heat and cools the heated tissue. Due to its high atomic number of 197Au, gold nanoparticles are excellent x-ray absorbers. This allows the element to have a higher mass, providing a greater area of absorption of x-rays. By acting as a contrast agent and injecting it into cancerous tumour cells, the cancerous tissue would be exposed to a higher dose during radiotherapy treatment²⁴.

Angiogenesis therapy:

Angiogenesis is a process in which new blood vessels are formed from pre-existing vessels. It involves the degradation, activation, migration, proliferation and differentiation of endothelial cells into vessels of the extracellular matrix. It is said to play a major role in cancer cell growth and spread. As a result of oxygen and nutrients, tumour progression occurs as a result of the transition from a tumour at the dormant proliferation stage to the active stage. This active stage leads to a cellular hypoxia state, resulting in increased regulation of proteins such as VEGF pro-angiogenesis. This results in the spreading alongside the newly created blood vessels of inflammatory proteins and cancer cells²⁴.

Drug vectorization:

Another way to use AuNPs in cancer therapy is as targeted drug delivery agents. Research shows that AuNPs can be easily operated and combined with a variety of molecules, including chemotherapy drugs such as doxorubicin²⁰.

A major complication with current chemotherapy treatment methods is that treatment is not optimized to specifically target cancer cells and the widespread distribution of chemotherapy drugs throughout the body can cause harmful side effects such as nausea, hair loss and cardiotoxicity .

Because many of AuNP's characteristics allow them to specifically target cancer cells and accumulate within tumour cells, these molecules can act as drug delivery systems that target tumours. These complexes dissociate and release the chemotherapeutic once inside the tumour microenvironment, allowing the drug to take effect and ultimately cause apoptosis.³¹

The advantages of gold Nano particles in drug vectorization. To effectively treat different types of cancers, they can pack several different sizes and types of dendrimers and several different types of ligands. Research shows, for example, that 80-90% of tumour cells in breast cancer have oestrogen receptors and 60-70% of tumour cells in prostate cancer have androgen receptors³⁰.

Other Applications:

Indirectly therapeutically, gold nanoparticles can be used. The angiogenesis issue describes the formation of new blood vessels that may not only increase the spread of cancer cells, but may also proliferate the spread of rheumatoid arthritis-responsible proteins. As AuNPs decrease angiogenesis, the result is reduced rheumatoid arthritis²⁴.

HIV:

Several AuNP valences have been found to inhibit HIV fusion. 2-nm AuNP-mercaptobenzoic acid has been combined with a derivative of a known CCR5 antagonist, a small molecule that antagonizes the CCR5 receptor, and CCR5 is commonly used to enter the cell by HIV. The antagonist of the CCR5 would bind to CCR5, leaving no binding spots for HIV. Ultimately, this will result in an effect that will limit HIV infection.

HEPATITIS B:

DNA gene samples prepared for AuNPs-Hepatitis B virus (HBV) could be used directly to detect HBV DNA. The detection-visualized fluorescence-based method is highly sensitive, simple, low cost, potentially applicable to multi-gene detection chips. The sample used here is essentially a biosensor to detect specific material.

TUBERCULOSIS:

Sensitive detection in clinical samples of Mycobacterium tuberculosis, the cause of human tuberculosis, was a successful application of the AuNP-nanoprobe colorimetric method to clinical diagnosis.

V.ADVANTAGES & DISADVANTAGES OF GOLD NANOPARTICLES:

ADVANTAGES:

1. Gold nanoparticles is simple for diagnosis.
2. It is non-toxic to human beings.
3. It is less invasive.
4. It provides increased contrast for diagnosis oral cancer.
5. It does not photo blinking which is inherent to many other fluorophores.
6. As compared to other metallic nanostructures, AuNP provide advantages of their simple and fast preparation and bioconjugation.

DISADVANTAGES:

1. It leads to acute or chronic toxicity.
2. Optical signals of AuNps may not be as strong as quantum dot.
3. It exhibits difficulties like biocompatibility, in vivo kinetics, and tumour target efficiency.[32]

CONCLUSION

Gold nanoparticles have revolutionized the medicine sector in some ways due to its wide-ranging applications in targeted drug delivery, imaging, diagnosis and therapy due to its extremely small size, high surface area, stability, non-cytotoxicity and adjustable optical, physical and chemical properties. Functionalized gold nanoparticles have been used in cancer therapy with various biomolecules such as proteins, DNA, amino acids and carboxylic acids and provide an excellent drug delivery system. Targeted delivery and scheduled release of therapeutic drugs to the specific site is achieved by using gold nanoparticles because they can carry a high drug load and release it to the specific site through different routes of administration and can interact with cancer cells. Conjugation with gold nanoparticles has minimized side effects of conventional drugs and increases patient's quality of life.

Competing Interest

All authors declare that they have no competing interests in this section.

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Author's Contributions:

All the authors read and approved the final manuscript

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