**Role of Gold Nanoparticles: Synthesis and their Applications For Cancer Therapy**

**Abstract**

The fast growth of nanotechnology in recent years has sparked a surge of interest in nanoparticle research, particularly in its medicinal applications. The frontiers of nanotechnology are continually being pushed back due to a rising body of information based on a better understanding of the characteristics of gold nanoparticles (AuNPs) and tireless testing. There appears to be a surge in interest in using AuNPs in cancer management, including diagnosis, monitoring, and treatment. These efforts are being made in the hopes of transforming present treatment approaches and strategies for cancer patients.These attempts are being made in the hopes of transforming present cancer treatment methods and strategies. The present uses of AuNPs in cancer care will be the subject of this review.

Keywords:- Nanopartiles

**1.Introduction**

According to the World Health Organization (WHO), cancer was the number one cause of death in the world in 2007, accounting for 7.9 million fatalities. Cancer deaths are anticipated to rise globally, with an estimated 12 million cancer deaths by 2030.[1]Other than surgery, the main therapeutic techniques for cancer treatment are chemotherapy and radiation therapy.In radiation therapy, energy is absorbed in the target area, destroying cancer cells or their vascular, causing tumour death or nutrient blockage.[2] In cancer treatment, a combination of radiation therapy and chemotherapy is used. Despite the efficacy of combined radiation therapy and chemotherapy in clinical trials, the fundamental constraint of combining chemotherapy and radiation therapy is normal-tissue toxicity, as each modality can induce severe normal-tissue toxicity.[3]The fundamental restriction of combining chemotherapy with radiation therapy is normal-tissue toxicity, as each modality can induce significant normal-tissue toxicity.[4]Gold nanoparticles (AuNPs) have excellent physical properties and customizable surface modification, making them a promising platform for creating cancer theranostics.

This article presents a comprehensive analysis of AuNPs as prospective nanomaterials for cancer theranostics in the future. The key physicochemical features of AuNPs, such as form, optics, and surface chemistry, are examined in this context. Furthermore, numerous AuNP-based diagnostic and phototherapeutic techniques are critically examined, with a focus on those developed to overcome transport limitations. [5,6]Among the current cancer treatments are surgery, chemotherapy, and radiation therapy. While these procedures have been approved and utilized for decades, they can have downsides and adverse effects. Surgical removal of tumors is limited mostly to large, resettable, and accessible tumors. Chemotherapeutic medications target fast dividing cells, killing not only cancer cells but also normal cells such as bone marrow cells and immune cells.[7]This usually causes "collateral damage" in the patient's body. Radiation therapy involves the use of high-energy radiation such as X-rays and gamma rays to eradicate tumour cells, which invariably has a negative impact on healthy tissues along the radiation route.[8] Typically, gold nanoparticles of controllable size and form have been manufactured by a variety of physical (microwave and ultraviolet (UV) irradiation, laser ablation), chemical, and biological methods.

Chemical synthesis generally involves the use of chemicals and solvents, both of which have environmental and human health consequences. In addition, it demands conditions like pH, temperature which are not optimal. [9,10]Many nanotechnology centers have been developed around the world in the last decade.[11]More than $6 billion has been invested in nanotechnology research in the United States alone, and more than sixty centers, networks, and facilities financed by various agencies are either operational or about to start.[12]Nanotechnology is projected to evolve into a clinically valuable field in the near future after the establishment of an inter-disciplinary nanotechnology workforce. Biomedicine is a key application of nanotechnology. By overcoming the numerous biological, biophysical, and biomedical barriers, nanoparticles can be designed as nanoplatforms for effective and targeted medication and imaging label delivery. The advantages of cutting-edge nanodevices (e.g., nanochips and Nano sensors) over traditional assay methods for in vitro and ex vivo applications are clear.[13]

However, several barriers exist for in vivo applications in preclinical and perhaps clinical use of nanotechnology, including biocompatibility, in vivo kinetics, tumour targeting efficacy, acute and chronic toxicity, ability to escape the reticuloendothelial system (RES), and cost- effectiveness. [14,15] In this review, we will describe the current state-of-the-art of gold nanoparticles in biomedical applications.

**2. Synthesis of Gold-Nanoparticles**

There are many subtypes of gold nanoparticles based on the size, shape, and physical properties. The earliest studied gold nanoparticles are gold nanospheres. Subsequently, nanorods, nano shells, and nanocages have all been reported. Another type of gold-based nanoparticles, with excellent surfaceenhanced Raman scattering properties (termed “SERS nanoparticles”), will also be discussed in this review. In the following text, the term “gold nanoparticle(s)” will refer to a collection of all these subtypes and the subtype of gold nanoparticles used in each study will be specified whenever possible. With continued development in the synthesis techniques over the last two decades, most of these gold nanoparticles can now be produced with well-controlled size distribution, sometimes with stunning precision.

**2.1 Gold nanospheres**

Gold nanospheres (also called as gold colloidal particles) with diameters ranging from 2 nm to over 100 nm can be manufactured via controlled reduction of an aqueous HAuCl4 solution under varied circumstances using different reducing agents. Citrate is the most often utilised reducing agent, and it can yield almost monodisperse gold nanospheres. The citrate/gold ratio can be changed to adjust the size of the nanospheres. In general, using less citrate results in larger nanospheres. The main drawbacks of this approach are the low yield and the requirement to use water as the solvent. [16] Gold nanospheres typically exhibit a single absorption peak in the visible range between 510 nm and 550 nm. The absorption peak shifts to a longer wavelength as particle size increases, and the width of the absorption spectra is proportional to the size distribution range. Many other forms of gold nanoparticles, such as nanorods, nano shells, and nanocages, have been investigated in order to produce optical characteristics suited for biomedical applications.

**2.2 Gold nanorods**

 The template method, which is based on the electrochemical deposition of gold within the pores of nanoporous polycarbonate or alumina template membranes, is commonly used to produce gold nanorods.[17]The width of the gold nanorod is governed by the pore diameter of the template membrane, while the length of the nanorod is controlled by the amount of gold deposited within the membrane's pores. Because only one monolayer of nanorods is generated, this process has a low yield. The most well-known approach for manufacturing gold nanorods can yield larger aspect ratios than other methods. [18,19]Typically, gold seeds are created by chemically reducing a gold salt with a strong reducing agent such as NaBH4. These seeds, which serve as the nucleation sites for nanorods, are then added to a gold salt growth solution including a mild reducing agent such as ascorbic acid and hexade-cetyltrimethylammonium bromide. The aspect ratios of the gold nanorods can be modified by altering the amount of gold seeds in relation to the gold precursor. Furthermore, with the addition of AgNO3, quantifiable yields of gold nanorods can be obtained. [18,20] Aside from the methods listed above, various other approaches to the production of gold nanorods have been examined, including bio-reduction [21], growth on glass [22], and growth on carbon [25]

**2.3 Sers nanoparticles**

SERS is an optical technique with various advantages over earlier technologies such as fluorescence and chemiluminescence, such as increased sensitivity, multiplexing, robustness, and performance in blood and other biological matrices. In a landmark study, gold nanospheres (13 nm in diameter) modified with Cy3-labeled, alkylthio capped oligonucleotide strands were used as probes to detect the presence of specific target DNA strands. Because of its broad Raman cross-section, the Cy3 group was chosen as the Raman label.[23]SERS nanoparticles have now been used in a number of other studies as well. Gold nanospheres with a diameter of 60 nm were encoded with a Raman reporter and stabilized with a thiolated polyethylene glycol layer in one study (PEG). Another type of SERS nanoparticle has a gold core, a Raman-active molecular layer, and a silica coating. Physical hardness, resistance to a variety of environmental conditions, and easy surface modification utilising silica chemistry are all benefits of the silica coating. Thiol groups can then be combined with maleimide activated PEG c on the silica shell. [24]

**3. Applications of nanoparticles**

 Over the previous decade, nanotechnology has been a popular issue. Material science and biology are two important areas of nanoparticle applications. In the field of material science, significant progress has been made. The fact that electronics are becoming quicker, better, and smaller on a monthly basis is plain and compelling evidence of such progress. However, nanoparticle applications in the biomedical field have fallen short of expectations. Only a few nanoparticle-based cancer diagnostic and therapy agents are in clinical trials or have been commercialized, and the majority of them are based on liposomes, which were created decades ago. Nanotechnology has a long way to go before it can truly change medical care as many have envisioned. Next, we'll go through the current state of gold nanoparticles in biological applications. Drug delivery methods based on gold nanoparticles provide a number of benefits over other nanocarriers and traditional medicines. Gold nanoparticles have been utilised as a cancer antigen and in tumour treatments for a long time.

Gold nanoparticles as drug delivery agents to cancer cells: Due to their simplicity of production, functionalization, and biocompatibility, GNPs are the finest nanocarriers for therapeutics. [23] GNPs are currently being investigated as potential drug delivery mediators for introduction into tumour cells in cancer therapy. [25] Through ligand receptor contact or non-specific methods, cells take up colloidal gold nanoparticles of various sizes and shapes [26]. Gold nanoparticles are coupled with suitable surface ligands that direct them only to cancer cells in order to validate the selective death of cancer cells. There have been two approaches for tumour targeting described: the first involved the conjugation of AuNPs to Polyethylene glycol (PEG), and the second involved the conjugation of AuNPs with a particular antibody that binds to biomarkers found on tumour cells. PEG decreased GNP agglutination and enhanced blood retention. The increased permeability of poorly differentiated blood arteries surrounding the tumour causes the accumulation of AuGNPs in tumour cells. Medication delivery systems (DDS) improve the solubility, in vivo stability, and biodistribution of a "free" drug. They can also improve the pharmacokinetics of some ‘free' medicines. Furthermore, putting a lot of drugs on DDS can turn them into a "drug reservoir," allowing for controlled and long-term release to keep the drug level within the therapeutic window.[27]

**3.1 Biomedical applications of gold nanoparticles**

Cancer nanotechnology, which includes molecular imaging, molecular diagnosis, targeted therapy, and bioinformatics, is an interdisciplinary field with extensive potential applications in the battle against cancer. Personalized oncology, in which genetic and protein biomarkers can be utilised to detect and treat cancer based on the molecular profile of each individual patient, holds promise as cancer nanotechnology advances. In vitro tests, in vitro and in vivo imaging, cancer therapy, and drug administration have all been studied with gold nanoparticles.[27]

**3.2 Gold nanoparticles applications in biosensor**

Gold nanoparticles that have been functionalized with a thiolated biomolecule have been used to create a biosensor that produces a shift in the optical absorption of GNPs after recognising complimentary biomolecules. When gold nanoparticles functionalized with antigen (antibody) are joined and the matching antibody (antigen) binds, the Plasmon absorption changes. [28]

##### **3.3 Gold nanoparticles applications for immunosensors**

Colloidal GNPs are the most popular nanoparticles for use in the lateral flows immunosensing (LFIS) approach. The LFIS method is based on immunological reactions in which an antigen is detected using a specific antibody that has been tagged with various markers such as GNPs and latex beads.[29] Depending on the method of detection, LIFS is classified as quantitative, qualitative, or semi-quantitative. Small analyte quantities are well detected by immunosensors. Using a colloidal gold and anodic stripping voltammetry, a new and practical electrochemical immunoassay for immunoglobulin (IgG) has been developed. The precipitation of silver on colloidal gold labels has been described using a novel electrochemical immunoassay. [30] The autolytic deposition of Au+3 onto GNPs improves the sensitivity of electrochemical immunoassay.

**3.4 Gold nanoparticle in cancer imaging**

The high absorption coefficient, potential biocompatibility, and low toxicity of AuNPs drew a lot of attention. In addition, AuNPs must be synthesized under specific conditions in order to alleviate concerns about potential toxicity caused by reducing agents and reaction conditions.[31]

The following are the key advantages of AuNPs in imaging applications:

* AuNPs have a long circulation duration in the body
* The enhanced permeability and retention (EPR) effect or surface modification with certain coatings cause AuNPs to selectively concentrate at regions of interest.
* AuNPs have a high absorption in the near-infrared window, making them ideal for photothermal therapy.
* Their simple functionalization.[32]

Because of the huge number of cancer patients around the world, it is critical to develop novel tools for early cancer detection. Because of the features of AuNPs, they can be used for optical imaging for a long period (i.e. photo resistance, stability). Furthermore, due to their unique interaction mechanism with light particles, these nanoparticles are effective contrast agents in optical imaging. Computed tomography (CT), photothermal/photoacoustic imaging, two-photon fluorescence imaging, optical coherence tomography (OCT), Raman spectroscopy, and light scattering imaging are the most used in vivo diagnostic techniques. [30,31] AuNPs with diameters of 30 to 100 nm often scatter intensely and can be easily spotted under dark-field illumination using a commercial microscope. [33] The scattering cross-sections of AuNPs have been reported to be 105–106 times greater than the emission of a fluorescent dye molecule.[34]

**3.5 Gold nanoparticle in cancer therapy**

For a variety of reasons, AuNPs are becoming more popular in medicinal applications. One reason is their ability to be generally non-reactive in biological environments, making them appropriate for in vivo applications. Furthermore, qualities like as strong optical behavior, easily adjustable surface chemistry that allows for variety in adding surface functional groups, and ease of control over particle size and shape during synthesis add to AuNPs' esteem. AuNPs are considered fully multifunctional as a result of these factors, and they provide the ability to combine multiple desired capabilities in a single molecular-sized package. [34,35]

**3.6AuNPs as antiangiogenic agents**

 Antiangiogenic properties have been observed for AuNPs. Although the specific mechanism of action is unknown, it has been discovered that AuNPs bind to vascular permeability factor/vascular endothelial growth factor (VPF/VEGF)-165 and basic fibroblast growth factor (bFGF) predominantly via the heparin-binding domain. [36] This has led researchers to believe that AuNPs can decrease angiogenesis in cancer cells by blocking the mitogens' downstream signaling effects on angiogenesis.[37]

**3.7AuNPs in radiation therapy**

 AuNPs have been found to be useful as radiosensitizers in a number of investigations (which are drugs that potentiate the effect of radiation for cancer therapy). In a study on mice with subcutaneous EMT-6 mammary carcinomas, AuNPs (1.9 nm in diameter) were found to have the ability to increase the efficacy of X-ray therapy, resulting in a remarkable survival rate of 86 percent, compared to 20% with X-rays alone and 0% with AuNPs alone.[38] However, whereas 1.9 nm AuNPs appear to have potential as radiation enhancers, evidence of acute cytotoxicity, DNA damage, and apoptosis driven by oxidative stress generated by cellular uptake of 1.9 nm AuNPs was recently observed [39]. When looking into the possibility of using AuNPs in radiation therapy to cure cancer, more research on cellular responses is needed. The ability of AuNPs to act as radiosensitizers appears to be linked to their surface functioning. While the research mentioned above used uncoated AuNPs, another study found that 5 nm AuNPs coated with the gadolinium chelating chemical dithiolated diethylene triaminepentacetic gadoliniumdid not exhibit radiosensitizing effect in both tumor cells in vitro and in vivo models.[41] Instead, a chemotherapeutic effect was seen, indicating that more research is needed. The authors speculate that the type of AuNPs' coating may have a significant impact on their radiosensitizing capabilities. The variance in radiosensitizing effects of AuNPs, on the other hand, could be ascribed to the varied diameters of AuNPs employed, as well as the type of tumour cells studied. [41,42]

**4.Conclusion**

Au NPs offer a lot of promise in terms of cancer treatment and drug delivery. Despite the fact that Au NPs aren't commonly employed in clinical applications, studies on Au NP-based medication delivery, gene therapy, photothermal therapy, and radiotherapy have all yielded promising findings, indicating that they could be viable alternatives in the future. Au NPs will undoubtedly continue to play an important role in enhancing the biomedical area, such as medication delivery and cancer therapy, based on current promising results and predicted progress in the future. However, some drawbacks to using Au NPs as nanocarriers or radiosensitizers, such as cytotoxicity, nonbiodegradability, and modification of cellular responses, should not be overlooked and should be thoroughly researched. Gold nanoparticles are used to provide targeted delivery and programmed release of therapeutic medications to a specific spot since they can carry a large amount of drug and release it to the specified site via multiple administration routes, as well as interact with malignant cells. Conjugation with gold nanoparticles reduces the side effects of traditional medications, improving patient quality of life.

**5. References**

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**Sphere Rod SERS**

**Figure 1: Different types of gold nanoparticles**