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A Review: Gold nanoparticles in biomedical anti-cancer applications

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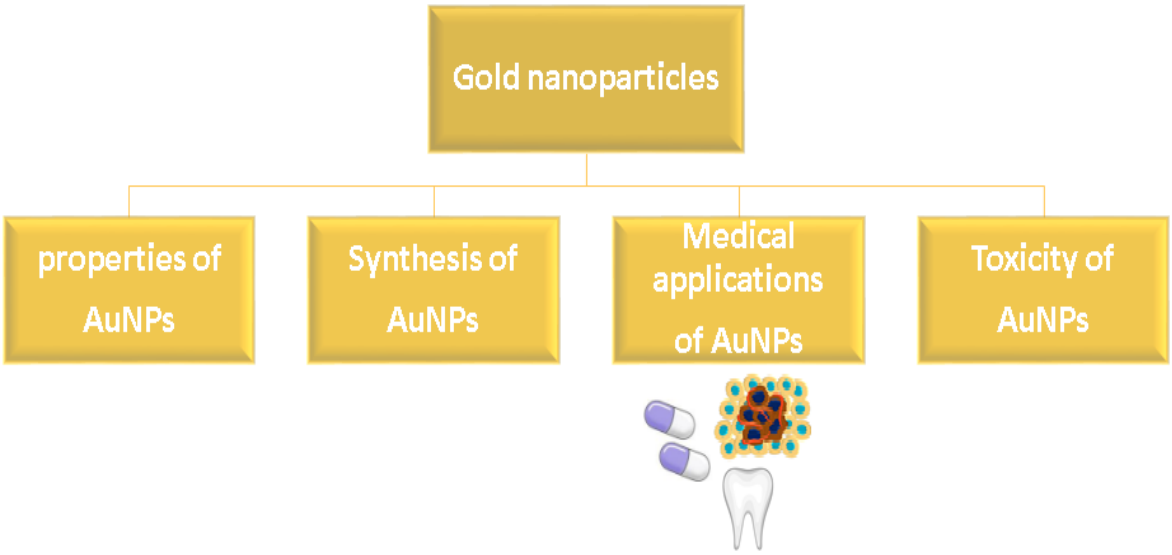

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Gold nanoparticles, Drug delivery, Photothermal, Photodynamic, Sonodynamic, Radiosensitizer therapy, Anticancer

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ABBREVIATIONS:

(AuNPs) gold nanoparticles
(PDT) Photodynamic therapy
(PTT) photothermal therapy
(SDT)Sonodynamic Therapy

ABSTRACT:

Gold nanoparticles (AuNPS) are highly promising organisms for solving a wide range of medical problems due to their special properties and low toxicity. The production of gold nanoparticles by biological method (green synthesis) is environmentally friendly and allows to reduce the amount of harmful chemicals and toxic products. This review is devoted to anticancer biomedical gold nanoparticle applications, and a variety of cancer types are mentioned, including lung, breast, cervical, liver, colorectal, and drug delivery mechanism targeting cancer cells. Other applications of these nanoparticles in vaccines, enzyme inhibition, vaccines, dentistry, and their work as metal sensors and others were also discussed.

1. Introduction

Cancer is a catch-all term for a group of genetic diseases. It is distinguished by uncontrollable random cell division. Cancer is frequently caused by mutations or changes in the expression patterns of primary oncogenes, tumor suppressor genes, and DNA repair genes. The majority of cancers are caused by environmental factors such as exposure to radiation and pollutants, but most importantly by an unhealthy lifestyle that includes a lack of physical activity, a poor diet, tobacco use, and stress. Only 5 10% of cancer cases are linked to inherited genetics. Cancer risk increases significantly with age, and many types of cancer are more common in developed countries [1][2] . Cancer is regarded as one of the leading causes of death worldwide. That's 14 million new cancer cases and 8.2 million cancer-related deaths, according to the National Cancer Institute (NCI). The number of new cases is expected to rise to 24 million over the next two decades, and approximately 40% of people will be diagnosed with cancer during their lifetime, it is known that cancer can be treated in several ways. Surgical removal, chemotherapy, radiotherapy (RT), or a combination of these three, depending on tumor size and location [3]. In addition to these primary procedures, secondary procedures such as photodynamic therapy, thermotherapy, sonodynamic therapy, and gene therapy are used to treat cancer. Among these methods, radiotherapy is a highly effective and noninvasive cancer treatment method. Four out of every ten cancer patients have received radiotherapy as part of their treatment. Radiation treatment plans in radiotherapy must be designed so that the damage to healthy tissue is kept tolerable for the patient while delivering a sufficient dose to the tumor [4].

In recent decades, many studies have been conducted on the use of organic and inorganic nanoparticles in all procedures associated with the diagnosis and treatment of cancer. Gold nanoparticles (AuNPs) are gaining popularity in a variety of fields of study due to their non-toxicity, biocompatibility, and unique properties. Gold (Au, atomic number 79) was discovered several thousand years ago and was one of the first metals to be discovered. Under standard conditions, it is a lustrous, yellow, dense, soft, and malleable metal in its purest form. Gold is one of the least reactive chemical elements. The high value of gold has been recognized since its discovery due to its rarity, ease of handling, workmanship, resistance to corrosion and other chemical reactions, and of course, its distinctive color. First, the characteristics of AuNPs will be discussed in this review. Some synthesized methods and then applications of AuNPs in various areas of cancer diagnosis and treatment are then listed.

2. Properties of gold nanoparticles

Gold-based materials have been used to treat diseases such as syphilis, epilepsy, rheumatism, tuberculosis, and a variety of inflammatory skin diseases [5][6]. It has also been used in recent years to diagnose and treat cancer in a variety of ways because of its distinct characteristics. The following are some of the unique properties of AUNPS:

• Simple synthesis in a variety of sizes and shapes [7].

• Surface properties of AuNPs: Due to AuNPs' reactivity with thiol and amino compounds, a variety of biological ligands, including DNA, peptides, proteins, antibodies, and viruses, can be used to coat the surface of AuNPs [8].

• Optical properties of AuNPs: Surface Plasmon Resonance (SPR) is a phenomenon related to the surface metal nanoparticles that give rise to the unique optical properties of AuNPs [9]. SPR occurs as a result of the oscillation of valence electrons in a solid when exposed to light. Following light absorption in nanoparticles, photons with the same frequency were emitted in all directions [10]. AuNPs' SPR properties allow them to absorb light in the near-infrared (NIR) and visible ranges. This property of AuNPs can be used in photothermal therapy and some optical imaging modalities.

• Good biocompatibility

• Nontoxic nature

• Comparative stability [11]

• Desirable endocytosis by mammalian cells [12]

• Low osmolality, even at high concentrations [13][14]

• Low viscosity, which allows convenient injection even into small vessels [14]

• Their high absorption coefficient, density, and atomic number make them an ideal agent for radiotherapy diagnostic and treatment stages. Following their synthesis, AuNPs can be easily characterized using a variety of methods, including 1. Determine the size distribution using a Dynamic Light Scattering (DLS) instrument. 2. Ultraviolet-visible (UV-Visible) spectrophotometry is used to assess the optical and electrical properties of nanoparticles. The maximum absorbance wavelength and optical density of a solution are affected by particle size and concentration [9]. UV–visible spectroscopy is used to verify the size and stability of AuNPs after they have been synthesized. 3. Direct imaging of AuNPs using Transmission Electron Microscopy (TEM) and Atomic Force Microscopy (AFM) to control features such as size, morphology, and surface coating [15]. 4. X-ray Photoelectron Spectroscopy (XPS) for characterization of GNP surfaces [16]. AuNPs have been extensively studied in various fields of cancer diagnosis and treatment due to their unique properties.

Figure 1 depicts the unique properties of AuNPs.

Fig 1: Unique properties of AuNPs

3. Synthesis of gold nanoparticles

Gold nanoparticles are the most important and common metallic nanoparticles, and they have been synthesized using a variety of physical and chemical processes. To create gold nanoparticles, a variety of biological, physical, and chemical synthesis techniques have been developed.

3-1 Biological

The biological synthesis of nanoparticles is a non-hazardous, dynamic, and energy-efficient method of producing nanoparticles. To synthesize NPs in vivo, this approach employs a variety of biological resources ranging from prokaryotes to eukaryotes. Metabolites found in these sources (proteins, fatty acids, sugars, enzymes, and phenolic compounds) play an important role in both the bioreduction of metallic ions to NPs and their stability. AuNPs produced biologically are more stable than those produced by other methods. Although AuNPs can be produced efficiently via chemical routes, the main risk is the generation of by-

products (secondary products) that are hazardous to human health and the environment. Many biological systems, such as plants, bacteria, yeasts, and bacteria, are therefore actively exploring new routes for the production of safe nano-products.

3.2 Green synthesis of plant extract -AuNPs

When compared to other environmentally friendly biological methods, nature provides a plethora of plants with the advantages of low cost, high reproducibility, eco-friendliness, and precision purification. The use of plant extracts as reducing agents and stabilizers in the preparation of gold nanoparticles has recently sparked interest due to their numerous benefits [17].

3.3 The general approach to plant preparation-AuNPs

It is a straightforward method that involves the selection of specific sections based on the type of plants. Collect, for example, the root part of the Euphorbia Fischer Diana plant, which is used as an antioxidant in general, the pulp part of Punicagranatum as an antimicrobial, the leaf of Allium noeanum as an antibacterial, and the juice of Papaya as L-Lys [17]. For example, after chemical therapy, cancer cells become insensible as a result of repeated drug administration; nanoparticles, on the other hand, are capable of increasing intracellular drug accumulation due to their ability to target and distribute more specific drugs [18]. Stabilizers and agents Plant extract biomolecules[19]. include polyphenols, flavonoids, sugar reduction, polysaccharides, alkaloids, amino acids, vitamins, ketones, phenols, and proteins. A plant that contains at least one of the aforementioned chemicals that reduces the metal ion to elemental metal must always be selected for biosynthesis. To prevent aggregation, first, reduce Au3+ to Au0, then meditate and stabilize AuNPs by covering the outer surface of gold. The diagrammatic representation of plant-based AuNP synthesis is shown in (**Figure 2).**

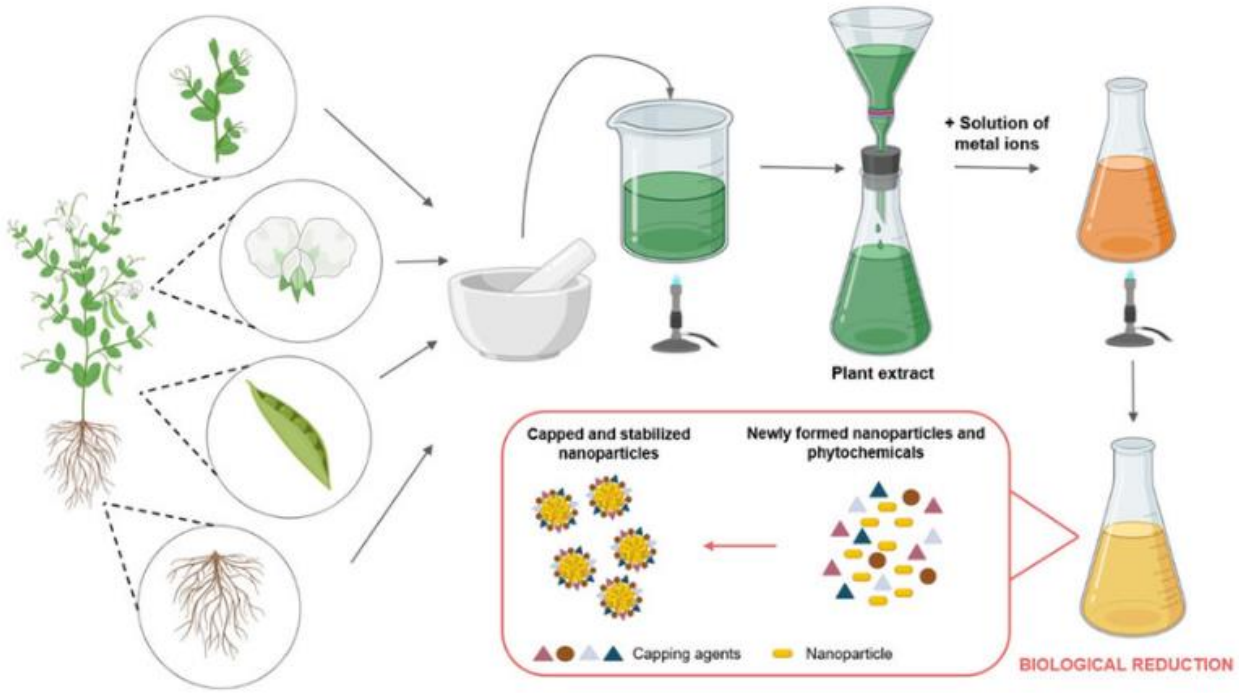

Fig. 2: Schematic representation of various parts of plant-based synthesis of AuNPs.

3.4 Physical

Several beneficial properties of spherical AuNPs have been identified, including size- and shape-related optoelectronic capabilities, a high surface-to-volume ratio, excellent biocompatibility, and low toxicity. It was discovered that the contact angle is heavily influenced by the size of the nanoparticles. The contact angle for de-ionized water droplets ranged from 24 to 67, and for DEG (droplet-based electricity generator droplets) ranged from 15 to 60, with nanoparticle sizes ranging from 14 to 620 nm. Surface plasmon resonance (SPR) and the ability to quench fluorescence are two important physical properties of AuNPs. Spherical AuNPs in aqueous solution exhibit a spectrum of colors (e.g., brown, orange, red, and purple) as the core size increases from 1 to 100 nm, with a size-relative maximum absorption between 500 and 550 nm. Furthermore, in aqueous environments, particles with high charges can cause double layers to form, and they can be discrete, dispersed, or suspended in the solution. The energy levels of electrons in a substance in nano-form are not as continuous as in bulk form. They are separated by the electronic wave function's confinement in up to three physical dimensions. This results in a change in surface area and electron containment; the change in material properties is controlled similarly to how melting point, fluorescence, electrical conductivity, and magnetic permeability are combining an ion coater on glycerin with a viscous liquid capture medium is a simple and direct method for producing uniform gold nanoparticles with a narrow size distribution. A low-cost, low-energy synthesis method that does not was necessitating the use of additives or reducing/stabilizing agents. It is based on a physical low vapor deposition method, as opposed to the traditional

hydration process of chemical reactions in liquids. The absorption spectrum showed a surface plasmon resonance peak at 530 nm during the formation of gold nanoparticles; the red-shift with increasing particle size indicated that gold nanoparticles were successfully developed using the ion coater [20]. Recently, researchers have focused on novel methods for synthesizing controllable particles of various shapes and sizes, **Figure 3** revealed that the AuNP's anatomy and physiology are associated with optical physical characteristics [21].

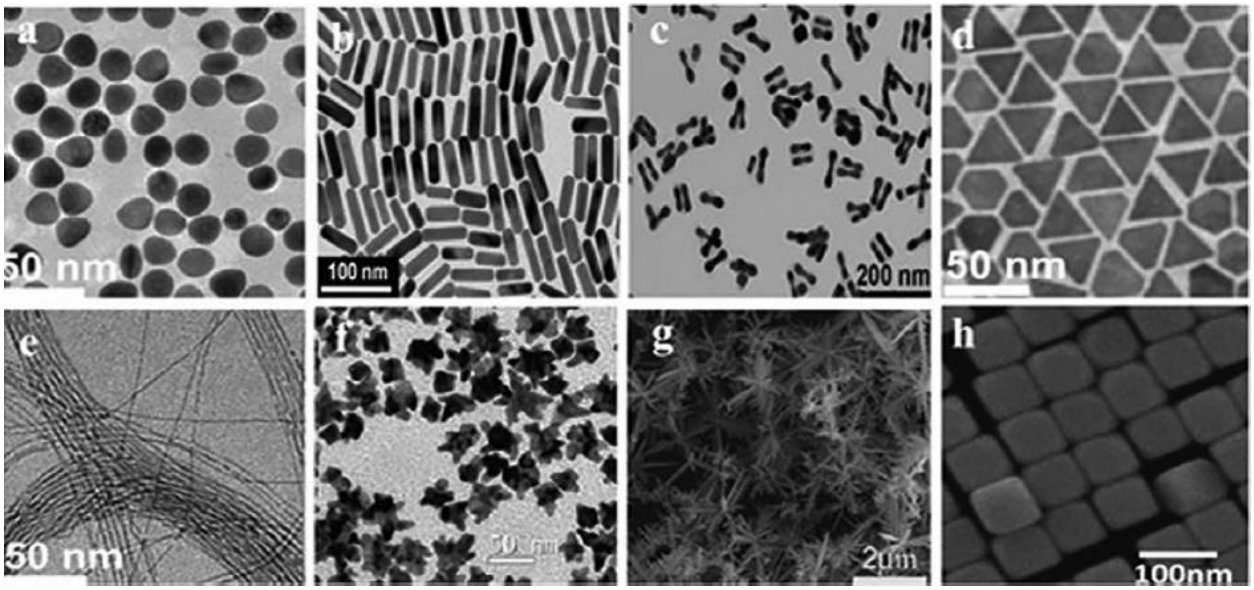

Fig.3: AuNPs TEM images: (a) quasi-spheres, (b) nanorods, (c) nanodumbbells, (d) triangular nanoprisms, (e) ultrathin nanowires, (f) nanostars; (g and h) AuNP SEM images: Nanodendrites (g) and (h) nanocubes.

3.5 Chemicals

Surface charge, surfactants, functionality, and stabilizers may be used in a specific application. The ultimate preferable state for nanoparticles is Au0 (non-oxidized state). Thus, the primary stage in the preparation of positively charged gold nanoparticles AuNPs is to reduce the oxidation of gold Au^{+1}(aureus) or Au^{+3}(auric) to Au^{0} by adding a reducing agent to the reaction, which is then vigorously stirred to form fairly uniform NPs in size. The AuNPs solution is then saturated, causing moderate precipitation. To reduce aggregate NPS, a stabilizing medium that adsorbs on the NP surface is typically used. The principle is the same, but there are several ways to accomplish it.

3.6 Turkevich-Frens method

This method, which was developed by J. Turkevich et al. to produce moderately colloidal AuNPs with sizes ranging from 10 to 20 nm, is used to synthesize AuNPs. The diameter of the shaped NPs can be altered by varying the amount of reactant used, as well as by using different styles or stabilizing factors. The main drawback was that only a limited number of AuNPs could be produced [22].

4. Application of AuNPs in cancer treatment

Gold nanoparticles can be used in a variety of applications, including air cleaning to remove odors and harmful carbon monoxide from rooms, water purification, energy cells, and critical medical applications. Since these particles can enter tissues due to their small size, one of the most important applications of these particles is their important role in cancer prevention, diagnosis, and treatment.

4.1 Drug delivery

The ability of nanoparticles (NPs) as drug delivery systems to carry drugs is 10 to 100 times greater than the molecular administration of drugs to tumors to improve diagnostic and therapeutic applications [23]. Furthermore, because of fewer uptakes by the reticular-endothelial system (RES), the drug circulation time within NPs can be increased, and it can augment drug uptake by tumor cells [24][25]. Because of properties such as biocompatibility, nontoxicity, and high affinity, the surface of AuNPs can be used for active tumor targeting with ligands, antibodies, and biomarkers capable of specific binding to tumors. Cytotoxic drug delivery at specific sites can improve diagnosis and treatment while reducing adverse side effects [8][26]. Some studies have reported the use of AuNPs to improve the therapeutic efficiency of anti-cancer drugs such as methotrexate[27]. tamoxifen[28], paclitaxel[29], and platinum-based drugs such as cisplatin and oxaliplatin[30][31].

4.2 Photodynamic therapy

Photodynamic therapy (PDT) is a novel treatment option for cancer treatment[25][32]. The PDT is founded on utilizing a photosensitizer that becomes after being irradiated with light Oxygen that is reactive Species (ROS) are produced as a result of light irradiation, because of the transfer of energy to the surroundings [8]. Traditionally, clinical photosensitizers Porphyrins and phthalocyanines are two examples of agents. Because of the lipid, hydrophobic substances are unable to enter cell membranes. As a result, they require a suitable carrier that can enter cancer cells without altering their structure agent. Indeed, in photodynamic therapy research, Nanoparticles serve as a vehicle for drug delivery[33]. Photosensitizer drugs Furthermore, the Nanoparticle adhesion to photosensitizing molecules ROS production can be increased by molecules[34][35]. PDT efficiency can be improved when conjugated with photosensitizer agents [25][33][35]. Khaing et al [33]discovered that using 5-aminolevulinic acid (5- ALA) bonded with AuNPs can increase the uptake rate of 5-ALA by

fibrosarcoma cells when compared to free 5-ALA. It has been reported that it causes a two-fold increase in ROS production. In addition, Mohammadi et al [35] reported that the presence of AuNPs (34nm) bonded with 5-ALA increases the uptake of 5-ALA photosensitizer drug by melanoma cells in PDT compared to 5-ALA alone. The results of an in vivo study suggested that the use of a designed gold nanoconjugate with 5-ALA would increase the efficiency of PDT compared to free 5-ALA. In different delivery systems, AuNPs covered by the PEG layer exhibit the highest efficiency for PDT drug delivery[32].

4.3 Photothermal therapy

AuNPs absorb light in the visible and near-infrared ranges, making them an excellent candidate for photothermal therapy (PTT). The temperature rises in the PTT method due to heat generation by AuNPs, which can cause cell death at temperatures above 50°C [11]. The temperature rises and light absorption in the NIR region are greater than in the visible region. Irradiation with NIR light excites electrons at various atomic levels, and when they return to a stable state, they emit energy as heat, which can raise the temperature of their surroundings. The shape of AuNPs affects scattering and absorption in the near-infrared region. Photothermal studies with AuNPs have shown that AuNPs shaped as nanorods, nanocages, and nanoshells have absorption peaks in the NIR region, whereas spherical AuNPs have a visible absorption peak at 530 nm[10]. Several studies have found that gold nanospheres are not as efficient as other shapes in terms of photothermal because their absorbance peak is in the visible rather than the NIR region [11]. The PTT method has been used successfully in the presence of AuNPs to treat cancer cell lines from the epithelial, breast, and colon, both in vitro and in vivo[36][37]. Hirsch et al. reported the use of silica nanoparticles coated with gold nanoshell for the treatment of human breast cancer cells by NIR PTT in vitro and in vivo [38]. Ghahremani et al discovered that microwave exposure increased the death of Saos-2 cells in the presence of AuNPs. They reported that increasing the size and concentration of AuNPs was a key factor in the improved efficiency of microwave thermal therapy. Mehdizadeh et al [39] conducted another study in which mouth epidermal carcinoma cells (KB cells) were treated with laser irradiation in conjunction with folate-conjugated gold nanorods. Salem et al [40] used laser irradiation with 5-FU-loaded chitosan-wrapped AuNPs to treat human hepatocellular carcinoma cells (HepG2). After 20 minutes of laser exposure, the 5-FU-AuNPs demonstrated enhanced light absorption with highly efficient photothermal conversion, resulting in a seven-fold reduction in the IC50 value.

4.4 Sonodynamic therapy

Sonodynamic Therapy (SDT) is a noninvasive cancer treatment method that employs ultrasound Cavitation can be caused by the accumulation of sonosensitizing agents in tumors followed by ultrasonic exposure in SDT. Acoustic cavitation has two modes: stable and transient. As a result of the acoustic cavitation phenomenon, ultrasound waves with high intensity and low frequency possess great curative potential. Bubbles grow several times

larger than their initial size during transient cavitation and then collapse. As a result, high mechanical and physiological stresses applied to the surrounding environment can be used to kill cancer cells [41]. Ultrasound irradiation had little effect on the tumor, but it was boosted by AuNPs. The CT26 cell line was used in an in vivo study. A significant difference was observed between the SDT+AuNPs group and other groups 13 days after treatment in terms of tumor volumes.

4.5 Radio-Sensitizer in radiotherapy

Almost 60% of cancer patients receive radiotherapy as part of their treatment. The use of radiation modifiers (protectors and sensitizers) before or shortly after radiation exposure is an important clinical method for reducing the effect of radiation on normal tissues and improving cell killing in tumors. High atomic number compounds containing elements such as iodine, which are used as contrast agents, can also act as radio-sensitizers. Unfortunately, cancer cells cannot absorb them selectively. Furthermore, they can cause anaphylactic shock, hypersensitivity, kidney failure, and selective iodine uptake within the thyroid gland [42]. AuNPs have distinct properties, particularly they're Because of their nontoxic nature and high atomic number, they are a good candidate for radiosensitizers. The action of AuNPs as a radiosensitizer has been investigated using simulation under inclement weather conditions in vitro and in vivo at low and high energies in several studies We will go over this in greater detail later subject in the sections that follow Before the submission of any AuNPs applications, application as a drug in clinical settings, toxicity and health effects on both targeted and non-targeted populations Tissues must be studied. It is critical to study. GNP toxicity and uptake because AuNPs are it is widely used in a variety of medical applications. The various applications of GNP in cancer treatment are summarized in (**Figure 4).**

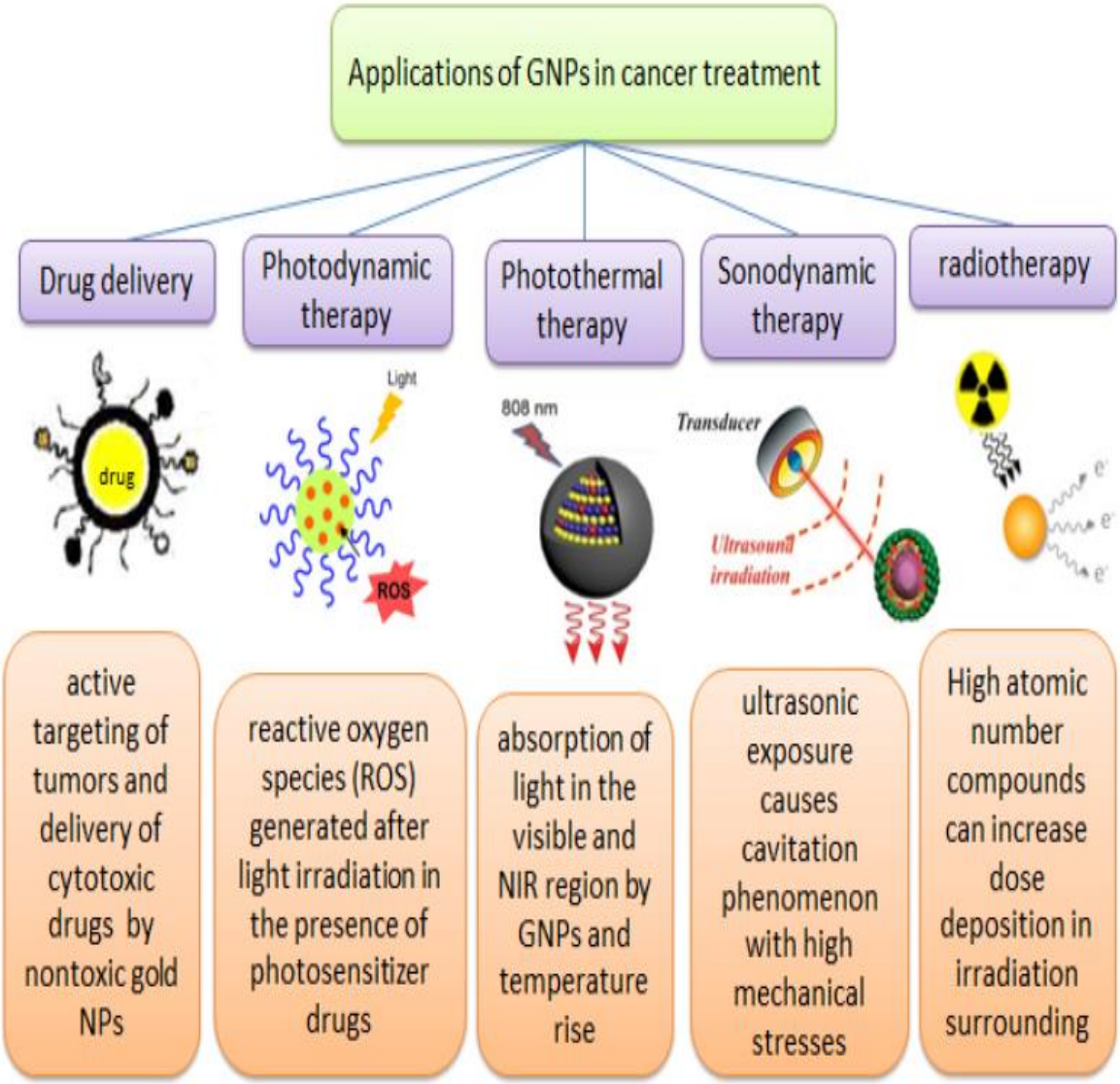

Fig 4: Different applications of AuNPs in cancer treatment

5. Gold nanoparticles in cancer management

5.1. AuNPs as drug delivery agents targeting cancer cells

AuNPs as drug delivery agents can increase the pharmacokinetics of the drug, thereby reducing non-specific side effects and achieving higher doses of targeted drug delivery. A prominent application of AuNPs is using them as vehicles for the delivery of molecules into cells. The payload can be a small molecule drug or a large biomolecule such as a protein, DNA, or RNA [43]. However, various factors need to be considered in designing an effective drug delivery system. The properties of AuNPs, such as their size, charge, and surface chemistry, have been shown to affect their uptake, as well as their subsequent intracellular fate. Gold nanoconjugates cetuximab and gemcitabine to be highly targeted in pancreatic cancer cells with high epidermal growth factor receptor (EGFR) expression [44]. Jiang et al prepared AuNPs with diameters from 2 to 100 nm and coupled them with trastuzumab using a citric

acid reduction method [45]. The results suggest that they target human epidermal growth factor receptor-2 (HER-2)-positive SK-BR-3 breast cancer cells. Better targeting is achieved, and cells have an obvious endocytosis effect on AuNPs with a diameter of 40 to 50 nm, while small-diameter AuNPs tend to separate from the cell membrane. Chen et al [46] used AuNPs of approximately 14 nm as the carrier linking with methotrexate (MTX) to study adverse reactions in vitro and anticancer effects in vivo. The results showed that compared with MTX alone, the coupling MTX of AuNPs can be rapidly and efficiently concentrated in tumor cells which significantly reduces the dose-dependent effect of efficacy [47]. Goel et al [48] also conducted a similar study and found that AuNPs can not only deliver drugs but also specifically infrared photothermal damage of tumor cells, which can be combined with near-infrared rays.

5.2 AuNPs application in tumor imaging

The most effective way to improve the prognosis of tumors is early diagnosis. In precision, intensity-modulated radiation therapy, such as 3-dimensional conformal radiation therapy and image-guided radiation therapy, accurate and clear images are important for the delineation of tumor target areas [49]. In recent years, many studies have attempted to use functional imaging to develop tumor radiotherapy plans. Although single photon emission computed tomography (SPECT) and positron emission tomography (PET) have higher sensitivity and specificity in distinguishing tumors from normal tissues, their spatial resolution is poor [50][51]. High spatial resolution is important in improving the tumor treatment ratio. The commonly used contrast agents are iodine agents, which have a short half-life in the blood (<10 min) and are less tumor-specific. With the rapid development of nanotechnology, the application of multifunctional nanoparticles in medical imaging has become important, such as iron oxide nanoparticles, carbon nanorods, AuNPs, and so on [6]. Among these nanomaterials, AuNPs have received increasing attention due to their mature synthesis, stability, and especially high X-ray absorption capacity . AuNPs are characterized by small size, good biocompatibility, and high atomic number, which means that AuNPs are potentially good contrast agents. At present, there are 2 ways in which AuNPs can target tumor cells: passive or active. Passive targeting uses only the osmotic tension effect (EPR) to converge in tumor tissue to form enhanced imaging [52][53]. Active targeting is the coupling of AuNPs with tumor-specific targeting agents, such as EGFR monoclonal antibodies, to achieve active targeting of tumor cells by GNP. When the energy exceeds 80 keV, the mass decay of gold is higher than that of iodine, which indicates that gold-nano is more advantageous in development [54]. Rand et al used mixed AuNPs with liver cancer cells and X-ray imaging and found that the liver cancer cell clusters in the gold-nano-mixed group were significantly more potent than the simple liver cancer cells. Using this new technology, tumors with a few millimeters in diameter in vivo can be detected, which is of great significance for early diagnosis [55].

5.3 AuNPs application in tumor radio sensitization

The distribution of AuNPs in tissues depends on their parameters, such as size and ability to inactivate tumor cells. Radiation therapy is widely used in almost all types of tumors, such as breast cancer [56]. The rays include X-rays, gamma rays, and high-energy particles. However, radiation therapy is indistinguishable between cancerous and normal tissues. Therefore, reducing normal tissue damage remains a limiting factor in radiation therapy [57]. Herold et al injected 1.9 nm AuNPs into breast cancer model mice and found that the tumor volume was reduced dramatically and the 1-year survival rate was higher after 2 minutes of irradiation (30 Gy) [58]. Stern et al injected AuNPs into the tumor site with radiotherapy and found that the tumor volume was significantly smaller and did not significantly expand with time [59]. Targeting AuNPs is a hotspot of the present research. By coupling chemical drugs or some biomacromolecules with AuNPs through chemical methods, it can play a role in reducing toxicity and increasing efficiency by changing the volume, mass, and charge of AuNPs [60]. Zhang et al constructed PEG-GNP conjugates from PEG using different diameters of AuNPs [61]. By coculturing with HeLa cells, Zhang et al [62] found that the amount of the conjugates entering cells was much higher than that of pure AuNPs. Khoshgard et al [63] synthesized folate and AuNPs to construct FA-GNP conjugates and co-cultured with HeLa cells with high expression of folate receptors and found that the uptake of FA-AuNPs by cells was much higher. Khoshgard et al found that the DEF (dose enhancement factor) co-cultured with FA-AuNPs was 1.23±0.09 times that of the simple irradiation group [48]. The results showed that the main uptake site was the cytoplasm, while the uptake of C225-AuNPs was much higher [64].

There is currently no clear conclusion about the mechanism of radio-sensitization of AuNPs. Jain et al co-cultured breast cancer cells with AuNPs under hypoxic, normoxic, and aerobic conditions and irradiated them. The uptake of AuNPs by cells under hypoxic conditions was higher than that under aerobic conditions. Under hypoxic conditions, the proliferation of breast cancer cells is also significantly reduced [65]. AuNPs showed better sensitizing effects under normoxia and moderate hypoxia. However, under the condition of a lack of oxygen, there is no significant sensitization. Yasui et al [66] concluded that AuNPs are mainly deposited in the cytoplasm and increase the expression of endoplasmic reticulum stress-related proteins by down-regulating DNA repair by inhibiting the expression of DNA repair-related proteins and promoting apoptosis [67].

5.4 AuNPs application in tumor hyperthermia

The thermo-therapeutic mechanism involves the initiation of heat stress in cells at 42 to 47°C, resulting in the activation of cells and/ or the initiation of intracellular and extracellular degradation mechanisms. The effects of hyperthermia on intracellular and extracellular processes include changes in signal transduction, induction of apoptosis, reduction of perfusion, and tumor oxygenation [68]. AuNRs or AuNSs has significant advantages for the absorption and scattering of near-infrared light (wavelengths from 650 to 900 nm). When exposed to electromagnetic radiation, especially near-infrared light, AuNPs can generate heat through surface plasmon resonance effects. Since the absorption peak of AuNPs is in the visible range (450– 600 nm), the absorption of near-infrared light by normal tissues is extremely small [44]. Stimulation of AuNPs by near-infrared laser irradiation induces

hyperthermia and minimally damages normal tissues. Therefore, gold nano-mediated thermo-therapeutics have the advantages of specificity and small trauma compared with traditional methods. In a mouse model of colon cancer, the researchers injected PEG-conjugated AuNPs into mice, and AuNPs were deposited on the tumor site and irradiated with near-infrared light at 800 nm. This treatment significantly prolonged the survival of the mice[69]. Moreover, the skin reaction in the normal part of the body was not different from that in the control group and only in the tumor site. Stuchinskaya et al found that AuNPs linked to anti-HER-2 antibodies can selectively target the killing of HER-2 over-expressing breast cancer cells after laser irradiation, indicating that AuNPs linked to antibodies are a kind of photothermal therapy and effective medium [70]. Huang et al found that the anti-EGFR antibody AuNRs can kill tumor cells at a lower laser power without causing normal cells to be damaged by high heat. Hainfeld et al [71] found that the tumor was completely ablated and that normal tissues were almost intact, in the photothermal treatment of rat tumors with modified cetuximab AuNPs. Wang et al covalently bound the nucleic acid aptamer CSC13 to the surface of AuNRs and targeted killed prostate cancer DU-145 cells and cancer stem cells under near-infrared light [72]. AuNPs absorb near-infrared rays, which accelerate the tumor temperature rise and can also be used to enhance tumor absorption of X-ray doses. The combination of hyperthermia and radiation therapy is synergistic. When the tumor was heated to 43.5°C with X-ray irradiation for 2 hours, the heat enhancement ratio is 8:1, making hyperthermia one of the most effective radiosensitizers [73]. However, tumor hyperthermia has certain limitations, such as poor specificity, difficulty in reaching deep tumors, and heat tolerance in the early stages [74].

5.5 AuNPs application in tumor gene therapy

Gene therapy is a new treatment that began in the late 20th century and provides an ideal way to treat cancer [75]. The targeted introduction of nucleic acids into tumor cells is a key process in gene therapy. Efficient transfection reagents must protect nucleic acids from nuclease degradation, and nucleic acids are released by cells and act in activated and released forms within the nucleus. AuNPs protect the surface of DNA from DNase I degradation [76]. On the 1 hand, due to steric hindrance, the enzyme cannot bind to the DNA on the surface of the particles and is not degraded by the enzyme [77]. On the other hand, a highly concentrated ion concentration around the DNA inhibits the activity of the enzyme. A synthetic non-viral nucleic acid delivery system such as a liposome has low immunogenicity but in general, has a problem of low delivery efficiency [78]. AuNPs have a large specific surface area and are easy to modify. They can be used as an ideal transfection reagent by loading a large amount of nucleic acid while regulating surface charge and enhancing water disposability, improving transfection efficiency and reducing toxicity [79]. Mitra et al [80] used epithelial cell adhesion molecule (EpCAM) monoclonal antibody as a targeting ligand and bound it to PEI-modified AuNPs. The results showed that siRNA-loaded AuNPs successfully entered RB cells and significantly reduced their viability. At the same time, control experiments showed that targeted siRNA-AuNPs significantly downregulated the expression of the EpCAM gene in RB cells compared to non-antibody-modified siRNA-AuNPs. Ghosh et al used cysteamine-modified AuNP-miRNAs, which are 10 to 20 times more efficient than liposomes and can effectively release miRNAs and downregulate the expression of genes [81]. Since the nucleic acid aptamer has a targeting function, it has become a hot spot for anti-tumor research. Ryou et al [82] used AuNPs to deliver RNA ligands specific for b-catenin

(which acts as a transcription factor in the nucleus) into HepG2 cells with higher transfection efficiency than liposomes. The results showed that the transcriptional activity of b-catenin in the nucleus was almost completely inhibited, and the mRNA levels of cyclin D and oncogene c-myc were decreased. In addition, they also ligated the RNA aptamer targeting the transcription factor NF-kB p50 to AuNPs. The results indicated that AuNPs could load aptamers into human lung cancer A549 cells and effectively induce apoptosis.

5.6 Other applications of AuNPs in tumor management

AuNPs can also be used as a stabilizer for other drug carriers, such as liposomes, and at the same time improves their delivery efficiency. The drug is susceptible to leakage in the plasma and other organs which limits its use [83]. Wang et al examined the adsorption of phospholipids by nanoparticles and demonstrated that nanoparticles can induce gelation at the liposome adsorption site. Since 25% of the outer surface of the lipid is occupied by the nanoparticles, the nanoparticle-modified liposome has no obvious leakage within 50 days of the solution [84]. Yang et al used AuNPs as stabilizers for oil-in-water emulsion droplets. They prepared a net negatively charged oil-in-water emulsion droplet with a particle size below 100 nm. The positively charged AuNPs bind to it via electrostatic interaction and then as a “bridge” to shield the strong repulsion between AuNPs and force. The results showed that the interaction between the AuNP-emulsion and AuNP-transferrin significantly improved the stability of the emulsion droplets [85][86]. In addition, AuNPs can also be used to promote the release of drugs. An et al embedded AuNPs in the middle of the bilayer of the liposome and used its photothermal effect to cause phase transition of the liposome bilayer to achieve drug release [87].

6 Different types of cancers

Due to space constraints, we have primarily focused on the most recent applications of AuNPs in solid tumor diagnosis and treatment, including lung, breast, cervix, liver, colon, and rectum crabs. AuNPs, on the other hand, have been used in the treatment of hematological malignancies such as acute myeloid leukemia (AML) [88] and chronic lymphocytic leukemia (CLL) [89]. Because of the unique properties of different AuNPs types, the use of AuNPs improved the efficacy of anticancer drug Treatments by increasing the amount of medication delivered to them Tumor.

6.1 Lung cancer

Some recent studies have reported the use of AuNPs for lung cancer diagnosis and treatment. Zhang et al. created AuNP-coated carbon nanospheres with an anti-carcinoembryonic antigen (CEA) antibody and used an ultrasensitive electrochemical cytosensing platform to diagnose nonsmall-cell lung carcinoma (NSCLC). In A549 lung cancer cells, the AuNP complex was nontoxic. Furthermore, the detection system was highly sensitive to A549 lung cancer cells, with a detection limit of 14 cells/ml. As a result, the findings of this in vitro study suggest that the AuNPs used to have the potential to detect early-stage NSCLC [90]. Shahhoseini et al. investigated the effects of combining 15 nm AuNPs

and ionizing radiation (IR) in human A549 lung cancer cells in vitro, focusing on the optical properties of AuNPs.Their findings showed that combining 1 mM AuNPs with 5 Gy of IR had a significantly greater inhibitory effect on cancer cell migration than IR alone. The anticancer efficacy of AuNPs and IR was due to water radiolysis, which increased ROS levels. The ROS were produced by the AuNPs' SPR [91].

6.2 Breast cancer

Breast cancer is the second leading cause of cancer deaths among women in the United States [92]. It has been shown that AuNPs could be used to treat breast cancer as a result of their localization in tumors, thereby decreasing systemic adverse effects and increasing efficacy [93][94]. Satish et al. synthesized AuNPs using HAuCl4 reduction and loaded the nanoparticles with curcumin, turmeric, quercetin, and paclitaxel. They then determined the efficacy of the AuNPs in MCF-7 and MDA-MB 231 breast cancer cells and the noncancerous cell line, HEK293. Their results indicated that the drug-bound AuNPs had greater efficacy than curcumin, turmeric, quercetin, and paclitaxel alone, and had lower toxicity in normal cells compared to breast cancer cells [95]. Dziawer et al [96] determined the efficacy of 211At-AuNP-PEGtrastuzumab in HER2-positive breast cancer cells in vitro. These investigators modified the surface of the AuNPs using polyethylene glycol (PEG), thereby allowing for the synthesis of AuNPs with trastuzumab, a HER2-specific monoclonal antibody. Their results indicated that conjugation with trastuzumab significantly increased the specificity and efficacy in breast cancer cells [96]. Significant results in breast cancer cells have been obtained by increasing the PTT and PDT efficacy of AuNPs. Liu et al. designed and synthesized functional chlorin gold nanorods coated with mesoporous silica, D-type cell-penetrating peptide (d-CPP), and Ce6. The mesoporous silica enhanced the attachment of Ce6 and d-CPP, which increased the cytotoxicity and apoptosis-inducing effects of PTT and PDT in MCF-7 breast cancer cells in vitro and in vivo, with 808 nm 2 W irradiation for 5 minutes in mice xenografted with MCF-7 breast cancer cells [97].

6.3 Cervical cancer

Cervical cancer is the world's fourth most common cancer in women. Several types of AuNPs have recently been developed to improve their in vitro and in vivo efficacy in cervical cancer cells. Catharanthus roseus (CR), a medicinal plant that is the primary source of vincristine and vinblastine, was used in the biosynthesis of CR-AuNPs [98]. In vitro data showed that CR-AuNPs (25–35 nm) were effective at killing HeLa cervical cancer cells (IC50: 5 mg/mL) [98]. Specifically, CR-AuNPs significantly increased caspase-3 and caspase-9 activity, as well as the expression of the proteins Bax and Bid. Increased levels of these proapoptotic proteins significantly increased the likelihood of apoptosis in HeLa cells [98].

6.4 Liver cancer

Currently, there are no highly efficacious treatments for liver cancer, which in 2016 alone caused approximately 27,000 deaths in the United States [99]. Therefore, there is a significant need for novel treatment regimens such as AuNPs. In human hepatoma HepG2 cells and normal peripheral blood mononuclear cells (PBMCs), Paino et al. compared the cytotoxicity of AuNPs capped with sodium citrate or poly amidoamine (PAMAM) dendrimers. Their findings showed that PMBCs were less sensitive to AuNPs than HepG2 cells, with HepG2 cell viability ranging from 70% to 80% with 0.01–50 mM citrate AuNPs and 50% to 70% with 0.01–50 mM PAMAM AuNPs.whereas the viability of PBMCs ranged between 60% and 80% with 0.01–50 mM citrate AuNPs and from 65 to 75 percent with 0.01–50 mM citrate AuNPs PAMAM AuNPs at 50 mM. This suggests that the AuNP drug-delivery system might reduce adverse effects if used for cancer therapy. AuNPs have also been used as carriers to produce highly sensitive probes for hepatoma detection. Li et al. used AuNPs conjugated with redox probes on carbon-coated nanotubes (CNTs) for a multi-analyte electrochemical immunoassay to simultaneously detect the liver-cancer biomarkers a-fetoprotein (AFP), a-fetoprotein variants (AFP-L3) and abnormal prothrombin (APT). The probes were immobilized by the AuNPs on the CNTs. By reducing nonspecific interactions, the conjugated AuNP probes significantly improved the detection of liver-cancer biomarkers.AuNPs have also been developed for potential use as a therapy for liver cancer.

Ashokkumar et al [100] investigated the anti-hepatoma efficacy of phytochemically synthesized AuNPs functionalized with Cajanus cajan extracts (CC-AuNPs). In vitro, CC-AuNPs killed HepG2 cancer cells in a concentration- and time-dependent manner, with an IC50 of 6 mg/ml after 24 hours of exposure. Mechanistic studies revealed that CC-AuNPs caused cell death by increasing ROS levels increasing ROS levels [100]. In vitro studies indicate that there is an abnormal expression of microRNAs, such as miR-300, miR-451, miR-345, miR-375, and miR- 326, in human hepatocellular carcinomas, and a decrease in the expression of miR-326 correlates with a poor diagnosis in patients with liver cancer [101]. Thus, it was postulated that mir-326might be an inhibitor of hepatocellular carcinoma. Mo et al. determined the therapeutic efficacy of miR-326-modified AuNPs in hepatocellular carcinoma Huh7 cells in vitro and in mice xenografted with Huh7 cells in vivo. The results indicated that the miR-326-modified AuNPs significantly decreased tumor-cell growth and volume. The efficacyofmiR-326 could be due, in part, to a decrease in levels of Akt, a protein that can promote tumor growth [102]. Similarly, Xue et al [102] determined the efficacy of miR-375-conjugated AuNPs. MiR-375 has been linked to spherical AuNPs with a diameter of ~36 nm via covalent gold–sulfur bonds. The AuNPs were shown to be a reliable delivery system for microRNAs and the AuNP conjugates induced apoptosis in HepG2 cells (~40% cell viability when incubated with AuNP-miR-375 at 100 nM for 48 h) and Hep3B cells (~50% cell viability when incubated with AuNPmiR- 375 at 100 nM for 48 h) and in mice tumor models. Overall, the stability and biocompatibility of the novel AuNP complex suggest that it might represent a promising therapeutic strategy for treating liver cancer.

6.5 Colorectal cancer

AuNPs are effective in various colon cancer cell lines and tumors in vitro and in vivo [103][104].

7. Other Applications of gold nanoparticles

7.1 Enzyme Immobilization

AuNPs have been used as enzyme immobilization matrices. The enzyme glucose oxidase was attached to AuNPs with a carboxyl-terminated thiol group and functionalized them [105]. The thermal stability of the immobilized enzyme was found to be greater than that of the free enzyme. Such immobilized systems have the potential to be very useful in a variety of biotechnological processes in the food and environmental fields. Hollow gold nanoshells entrapping horse radish peroxides have been synthesized to detect small molecules that can enter the nanoshells [106]. This method keeps the enzyme active in nanoshells, which makes it useful for a variety of biotechnological applications. Bi-enzyme functionalized magnetic nanoparticles were created by combining three layers of nanoparticles made of Fe3O4 magnetic core, Prussian blue interlayer, and gold nanoshell with the enzymes hydrogen peroxide and glucose oxidase [107]. This biosensor was tested using carcinoembryonic antigen (CEA) and -fetoprotein (AFP) as model systems, resulting in an amplified signal in terms of electrochemical activity and enzyme catalysis. An external magnetic field can be used to regenerate these magnetic nanoparticles. A biosensor of this type offers a wide range of detection methods with high reproducibility and sensitivity.

7.2 Immunoassay

AuNPs functionalized with antibodies such as human IgG and antibodies against pathogenic bacteria have been used in a variety of immunoassays [108][109]. Immunosensors that use single-chain fragment variable recombinant antibodies (scFv) rather than traditional monoclonal or polyclonal antibodies have recently been developed **Figure 5.**

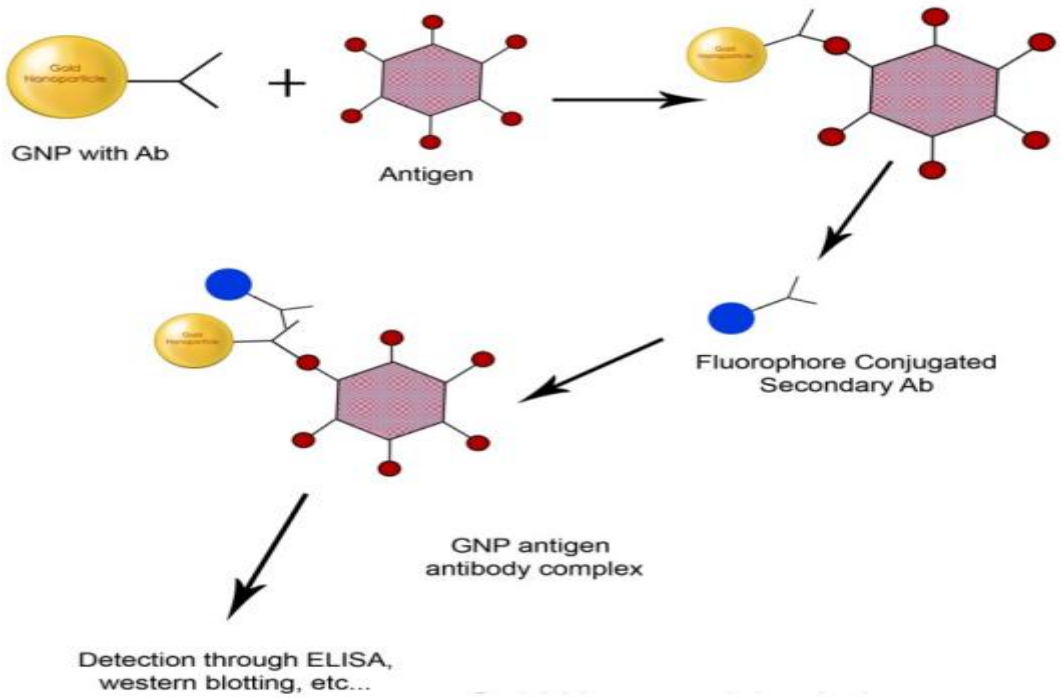

Fig 5. Antibody functionalized AuNPs for use in immunoassay.

ScFvs are small heterodimers composed of antibody variable heavy (VH) and light (VL) chains linked by a peptide linker that serves to stabilize the molecule. ScFv antibodies have several advantages over F_{ab} antibodies, including smaller molecular size, higher labeling fidelity, unique designs, and the ability to be mutated as needed. They also represent the smallest proportion of the antibody required for antigen binding. A colorimetric immunoassay was developed using AuNPs functionalized with engineered scFv containing either cysteine or histidine in its linker region [110]. To expose specific amino acids, scFv can be mutated and assembled using the phage display technique. Mutated scFv fragments exposing cysteine residues were found to form gold-thiolate bonds. These were also discovered to adsorb on the gold surface, forming a monolayer that provided an appropriate orientation for antigen binding. These biosensors based on AuNPs of size < 60 nm were found to be as sensitive as, if not more sensitive than, traditional fluorescence-based biosensors. When rabbit IgG is added to these scFv-cys stabilized AuNPs, the color changes from red to purple. The method was discovered to be highly efficient, sensitive, and with an extremely low detection limit. Similarly, another biosensor based on engineered recombinant A10B scFv has been developed for the detection of protein A as a model through self-assembled monolayer formation detected using AuNPs coated with protein A, with a 42-fold increase in detection limit when compared to A10B F_{ab} [111].

7.3 SNP Detection

Single nucleotide polymorphisms (SNPs) have by far been the most appropriate method for the detection of point mutations or polymorphisms in various genes, which can be easy, detected using complementary single-stranded DNA molecules **Figure 6.**

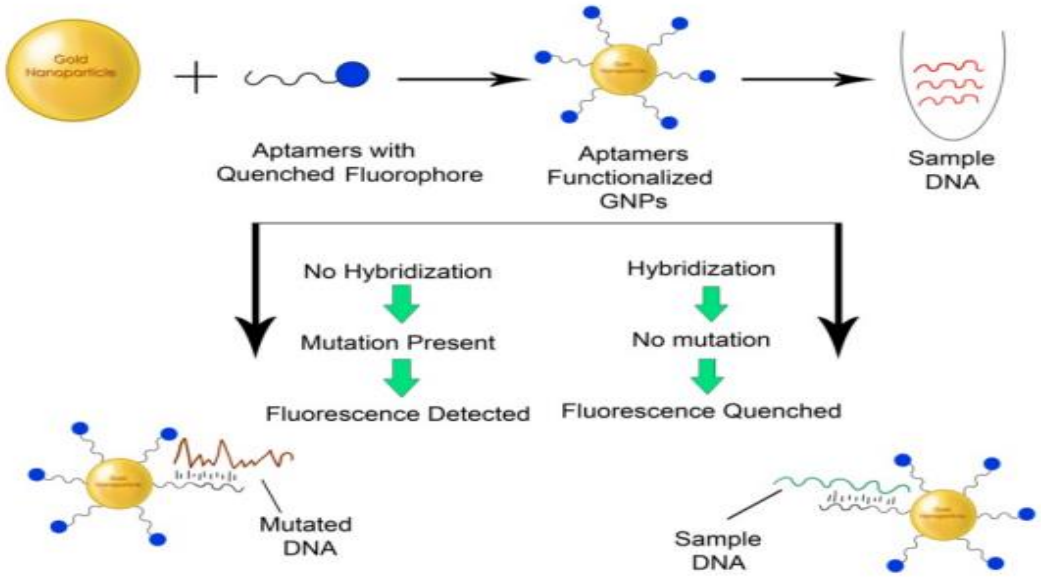

Fig 6. AuNPs functionalized with ssDNA for Single nucleotide polymorphism (SNP) detection.

SNPs are often associated with disease detection including diabetes mellitus, β-thalassemia, etc. AuNPs functionalized with single-strand-specific nucleases have been used to detect SNPs [112]. Likewise, a simple colorimetric assay was developed using DNA-functionalized AuNPs to detect SNPs in the human p53 gene [113]. This was successfully used to detect 12-point mutations in the human p53 gene as compared to wild type method showing a simple approach toward the detection of altered nucleotide sequences. This method neither needs complicated modification of AuNPs or DNA, nor additional requirement of DNA probes, signal amplification, or temperature control thus providing advantages over currently available methods.

7.4 Metal Sensors

The DNAzyme-AuNPs system was used to develop an easy colorimetric assay for detecting uranium [114]. Traditionally, complex biophysical techniques such as fluorimetry, ICP-MS, and atomic absorption spectroscopy have been used to detect uranium in the environment. These methods, however, are difficult to implement on-site. The DNAzyme-GNP system is a viable alternative to traditional methods. DNAzymes are in vitro-created catalytic DNA molecules with specific affinities to metal cofactors such as Uranyl ($UO2^{2+}$), the most common bioavailable form of uranium. These biosensors detected uranium in two ways: by disassembling DNAzyme functionalized AuNPs in the presence of uranyl ions, resulting in

a visible color change from purple to red ("turn-on" method), or by "turn-off" method, which was based on different adsorption properties of single and double-stranded DNA on AuNPs in the presence of uranyl ions. The method was significant because it detected uranyl at levels lower than the maximum contamination limits set by the US Environmental Protection Agency. Based on the shift in the surface plasmon resonance of AuNPs with aggregation of nanoparticles by sandwich complexation, AuNPs functionalized with aza-crown ether acridinedione were developed as a fluorescent chemosensor for metal ions [115]. Mercury ($Hg^{2+)}$ was detected using AuNPs functionalized with L-cysteine. In the presence of UV light and Hg2+, these AuNPs tend to aggregate resulting in their detection and making them useful biosensors for on-site applications [116]. Similar biosensor for Hg2+ detection was developed using oligonucleotide fAuNPs [117].

7.5 In Microscopy

Functionalized AuNPs have found their usage in electron microscopy [118]. The problem of the limited resolution of Cryo-electron microscopy single particle analysis due to poor alignment of samples can be obviated by using two-dimensionally arranged protein arrays labeled on AuNPs through genetic tag sites on proteins. AuNPs functionalized with nickel-nitrilotriacetic acid were used and Mycobacterium tuberculosis 20S proteasomes with 6x-histidine tags were assembled into 2D arrays and were used for three-dimensional reconstruction of biological macromolecules.

7.6 In Vaccines

AuNPs conjugated with carbohydrates and proteins have been used in novel vaccine development approaches, as the glycol-conjugated AuNPs act as a scaffold for carrying a large number of carbohydrate derivatives. Glyco-conjugated AuNPs (1–5 nm) capped with carbohydrate-based antigens found in cancer cells, such as Thomsen-Friedenreich disaccharide [119], sialyl-Tn and Lewis-Y [120], were tested for immune response and found to have a significantly higher immune response than the corresponding free carbohydrate.

7.7 therapeutic agents in pathologic angiogenesis

AuNPs have been shown to inhibit pathological angiogenesis in the retina, a leading cause of blindness. When compared to control animals, intravitreal administration of AuNPs significantly inhibited retinal neovascularization in a mouse model of oxygen-induced retinopathy of prematurity [121]. Histological examination revealed no differences in retinal thickness, inflammation, or cytotoxic effects on retinal cells in AuNPs-treated animals versus vehicle-treated groups. 134 Reva et al investigated the effect of subcutaneous AuNP injections on dermal structures in male CBA mice [122]. Injected nanoparticles were phagocytosed by macrophages, and AuNPs' anti-angiogenic activity was mediated by the toxic activity of nanoparticle-loaded macrophages. AuNPs' cytotoxic activity on vascular endothelium in subcutaneous tissues was mediated by the deactivation of macrophages that produce VEGF-A or by direct death of the endothelium as a result of macrophage migration through the vascular wall [122]. AuNPs treatment of normalized tumor vasculature in a human colorectal carcinoma xenograft nude mouse model (CRC) [123]. Treatment reduced

VEGFR2 and HIF-1 expression, which was accompanied by decreased vessel hyperpermeability and hypoxia, respectively. Furthermore, AuNPs treatment reduced plasma levels of anterior gradient 2 (AGR2), a biomarker associated with cancer progression and angiogenesis. Surprisingly, effects on tumor vasculature were found to disappear by day 14 of AuNPs treatment, implying a time frame for AuNPs' anti-angiogenic effects.

Other studies have demonstrated that AuNPs could enhance angiogenesis in animal models. The application of AuNPs in photo-bio-modulation therapy (PBMT) accelerated cutaneous wound healing in Sprague Dawley rats. Histological results indicated that AuNPs and PBMT are effective in stimulating angiogenesis and triggering inflammatory response at an early stage due to enhanced epithelialization, collagen deposition, and fast vascularization [124]. In addition, AuNPs increased the expression of CD31 endothelial markers and enhanced angiogenesis in an orthotopic co-implantation model of pancreatic cancer [125]. Roma-Rodrigues et al demonstrated modulation of angiogenesis using AuNP-peptide conjugates in CAM assay [126]. Specific peptide conjugates on the surface of AuNPs were observed to promote or inhibit angiogenesis in CAM assay by interacting with endothelial cell angiogenic receptors or by altering the balance between pro- and anti-angiogenic factors [126].

7.8. In various dental applications

7.8.1 Dental diagnostics

To improve the biorecognition process and overall bioreceptor performance, nano bio receptors were introduced, incorporating nanotubes, nanowires, and nano-dots in the sensing assembly. Replacing micro-sized particles with nanosized ones transforms the biosensor into a nano biosensor, with the advantage of rapidly identifying targeted biological tissues at an ultra-low molecular level. Its high sensitivity is particularly useful in cases of cancer diagnosis for example, as nano biosensors in comparison to conventional biosensors can detect cancer cell molecules at very early stages and in very low concentrations [127]. Nanobiosensors are also mechanically compliant, as they are easily displaced and deformed in response to very low forces, therefore, sensitive enough to detect the breaking of chemical bonds [128]. This is attributed to its nano-size effects, as the high surface area to core ratio increases the level of sensitivity, electrical properties, and response time of the biosensor [129].

7.8.2 Preventive dentistry

A nano-toothbrush has been devised by placing nano-colloidal gold or nano-silver particles between toothbrush bristles [130]. In addition to its ability to improve mechanical plaque removal, researchers have discovered that added gold or silver has an antibacterial effect, which may eventually lead to a significant reduction in gum disease. According to the study, oral hygiene products such as toothpaste and mouthwash solutions were also modified. Nano-calcium fluoride, for instance, was added to mouthwash products to reduce caries activity, reduce dentine permeability, and increase labile fluoride concentration in oral fluid. Toothpaste containing calcium carbonate nanoparticles and 3% nanosized sodium

trimetaphosphate has been reported to promote remineralization of early carious lesions in comparison to conventional toothpaste with no nano-additives. According to results from an in vitro study, toothpaste containing nano-hydroxyapatite crystals (nHA) significantly increased microhardness values in human enamel following an erosive challenge, in comparison to the same toothpaste without nHA [131].

7.8.3 Dental materials

7.8.3.1 Prosthodontics

Incorporating 0.4% TiO_2 nanoparticles into a 3D printed poly-methyl methacrylate (PMMA) denture base to improve its antibacterial characteristics and mechanical [132]. According to measurements using Fourier Transform Infrared Spectroscopy (FTIR), Scanning Electron Microscopy, and tests for antimicrobial efficacy against Candida species. The addition of zirconium oxide nanoparticles significantly improved the hardness levels, flexural strength, and fracture toughness of the heat-cured PMMA denture base. Nano-sized fillers were used due to their superior dispersion properties, less aggregation potential, and biocompatibility with the organic polymer.

7.8.3.2 Endodontics

Applications of nanotechnology in endodontics include the incorporation of bio-ceramic nanoparticles such as bioglass, zirconia, and glass ceramics in endodontic sealers. It has been found that the use of nano-particles enhances the adaptation of the adhesive to nano-irregularities, in addition to its fast setting time in comparison to conventional sealers, its dimensional stability, insolubility in tissue fluid, chemical bond to tooth tissue, and osteoconductivity. This was corroborated by a recent study, testing the antibacterial effects against endodontic biofilm, bond strength to dentine, and the ionic release of calcium and phosphate when a novel bioactive endodontic sealer was used [133]. The sealer was a mix of dimethyl amino hexadecyl methacrylate (DMAHDM), 2-methacryloyloxyethyl phosphorylcholine (MPC), and amorphous calcium phosphate nanoparticles (NACP)

7.8.3.3 Periodontics, Implantology, and regenerative dentistry

Scientists were able to create a novel drug delivery system for the treatment of periodontal disease, through triclosan or tetracycline-loaded nanoparticles. These nanoparticles are uniformly dispersed within a matrix, which gradually biodegrades, releasing loaded drugs in increments to provide a longer contact duration with the diseased site. Niosomes, for instance, are chemically stable non-ionic vesicles, which offer a controlled and targeted drug delivery with enhanced penetration through biological tissue especially when the particles are less than 100 nm in size.

8. Challenges of AuNPs in clinical applications

Although AuNP-assisted PTT and PDT have demonstrated promising benefits in cancer treatment in vitro and in vivo in a variety of cancers, several obstacles must be overcome before such treatments can be translated to the clinic. Cytotoxicity is a particular challenge, especially when long-term treatment is contemplated. Despite some evidence that AuNPs are biocompatible, cytotoxicity caused by AuNPs treatment could be caused by surface ligands and laser damage [94]. Another issue is biodistribution, as AuNPs can accumulate in the liver and spleen, where some studies have shown the toxic effects of AuNPs [134]. Furthermore, due to the requirement for localized activation, AuNPs may have limited clinical utility in the treatment of metastatic and recurrent cancer [135].

9. Toxicity of AuNPs

Several studies have raised questions about the toxicity of these nanoparticles. AuNPs toxicity is influenced by physicochemical properties such as size, charge, shape, and surface chemistry. An in vitro study revealed that AuNPs protected with $Ph_2PC_6H_4SO_3Na$ and $P(C_6H_4SO_3Na)_3$ ligands were toxic to different cell lines in a size-dependent and cell type-independent manner. The cytotoxicity of 1.4 nm AuNPs was up to 60-fold higher than that of 15 nm AuNPs [136]. The same working group later found that 1.4 nm triphenylphosphine mono sulfonate-coated AuNPs cause reactive oxygen species generation, up-regulation of stress and inflammation-related genes, mitochondrial permeability transition, and then cell death in HeLa human cervix carcinoma cells [137]. Another study demonstrated that 1.4 nm AuNPs were able to bind to the DNA of both healthy and cancerous cells [138]. Mironova et al. demonstrated that neither 13 nm nor 45 nm AuNPs enters the nucleus or mitochondria of human dermal fibroblasts, instead remaining in cytoplasmic vacuoles and that 45 nm particles caused more cell damage due to their different uptake mechanism and thus increased cytoplasmic release [139]. Particle shape is also important. A study found that the cellular uptake of spherical AuNPs is greater than that of rod-shaped AuNPs [140]. Toxicity is also affected by charge, as demonstrated by Goodman et al experiments, which revealed that positively charged particles were more toxic than negatively charged particles [141].

Other research suggests that surface chemistry, rather than charge, is more important in the cytotoxicity of AuNPs. Positively charged poly(diallyl dimethylammonium chloride)-coated AuNPs were found to be more biocompatible with cell membranes than positively charged cetyltrimethylammonium bromide-coated AuNPs [142]. Exposure time and concentration are also critical parameters. In vitro research revealed: a) toxicity increased proportionally to GNP concentration [139][141][143], b) cytoskeleton filaments of cells can recover within 14 days after stopping exposure to AuNPs [138], and c) both chronic and initial acute exposures to AuNPs at a low dose can induce modifications at the gene level after 20 weeks [144] Several in vivo experiments were carried out to assess the systemic toxicity of AuNPs. Here too, GNP properties are key parameters in toxicity. Studies showed that size and charge can affect the absorption and biodistribution of AuNPs in the animal model. The smaller and negatively charged particles seem to have the highest absorption rate and the

widest organ distribution [145][146]. AuNPs surface coating and shape were also proven to influence biodistribution in vivo [147][148]. Other research has found that AuNPs, regardless of charge or surface chemistry, tend to accumulate in the liver and spleen [149][150]. Kidneys appear to be especially vulnerable to GNP exposure. An experiment revealed that AuNPs altered renal tissue in a size-dependent manner, with smaller particles causing more damage [151]. The route of administration can also affect the toxicity and fate of AuNPs within the body. An in vivo study revealed that the toxicity of AuNPs is higher after oral and intraperitoneal administration than after tail vein administration [152]. AuNPs' embryotoxicity and genotoxicity have also been studied. In zebrafish embryos exposed to cationic N, N,N-trimethylammoniumethanethiol-capped AuNPs, eye development, and pigmentation were disrupted, followed by behavioral and neuronal damage [153]. An in vivo study in Drosophila melanogaster revealed a mutagenic effect of 15 nm naked AuNPs. Phenotypic modifications in the subsequent generations of Drosophila proved AuNPs' capability to cause mutagenic effects that may be transmitted to the progenies [154].

Conclusions :

In summary, AuNPs have distinct optical and surface properties that distinguish them from other nanoparticles, allowing for their potential use in the diagnosis and treatment of cancers such as lung, breast, cervical, liver, and colorectal cancer. Despite promising preclinical results, several issues concerning biosafety and adverse/toxic effects must still be addressed. Future research will be needed to determine the immunological response to AuNP formulations as well as their pharmacokinetic profile.

Given the extraordinary interest in the development of transition metal complexes, the horizons can be expanded by using amazing and highly promising nanoparticles such as platinum and palladium as potential antitumor agents and to solve a wide range of medical problems, so the content can be directed towards future developments of platinum and palladium complexes.

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