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Gold Nanoparticle: Synthesis, Functionalization, Enhancement, Drug Delivery and Therapy: A Review

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ASTRACT
The excellent properties and advantages of golden nanoparticles are copyrighted by a number of publisher roles. There are different physical, chemical and biological methods possible in preparing colloidal or suspended nanoparticles with pharmacodynamic and optical properties. The surface of golden nanoparticles plays an effective role in improving performance and efficacy as a carrier of nanoparticles of many drugs, especially in the field of cancer treatment. Despite the difficult challenges faced by gold nanoparticles in the field of drug delivery, these molecules are a great opportunity as a treatment and nano carrier to deliver drugs to anticancer, antibiotic, vaccine and genetics, so a comprehensive study must be conducted to find out all the pharmacokinetics and cytotoxic properties of cells for long periods.
Keywords: Gold nanoparticles AuNPs, pharmacological, inorganic nanoparticles
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INTRODUCTION

The goal of pharmaceutical dosages is to enhance the dynamic capacity of treatment and are protected by the rights to be written and preserved. Therefore, this kinetic capacity of the drug must be increased using nanoparticles and is a molecule of size less than 100 nanometers [1-4]. In 1857 Faraday and others first prepared colloidal gold which is a solution or suspension of nanoparticles of gold nanoparticles in a liquid, most of which is water by reducing gold chloride with phosphorous and produces an intense red or colloidal color of blue / purple gold [5-9].

During the 20 th century, procedures like TEM (transmission electron microscopy) and AFM (atomic force microscopy) allowed the precise imaging of nanoparticles. Gold nanoparticles AuNPs(GNPs) are inorganic nanoparticles consist of a gold atom inner core and negative groups on the surface [10-15]. The surface can be simply functionalized for active targeting by adding a monolayer of surface ligands. In addition, they can be modified by different chemical and physical methods, AuNPs (GNPs) for biomedical uses are mainly synthesized using the colloidal preparation method using a gold metal precursor, a reductant, and a stabilizer [16,17]. This methodology permits accurate control of the optical and electrical properties that powerfully depend on the size scale from 1nm to 100 nm and various shapes as nanosphere, nanocage, nanoshell, and nanorod of the produced AuNPs(GNPs) [18-22]. GNP's innovative drug delivery systems have many benefits over other conventional as well as to nanocarrier drug delivery systems. Some of these advantages are enumerated here; (a) GNPs have characteristic optical, physical, and chemical properties due to their different size and shape. (b) GNPs provides high drug loading capacity due to high surface area (c) GNPs are readily available for biofunctionalization with biomolecules such as proteins, enzymes, carboxylic acid and DNA and are biocompatible; (d) GNPs have controlled uniform dispersity; (e) Due to nano-scale and uniform dispersion of GNPs they can reach to the targeted site of action with blood flow easily, They are safe and noncytotoxic to the normal cells and (f) GNPs are easily synthesized by different methods of synthesis. Challenges of GNP as a nanocarrier drug delivery system are (a) Factors affecting biodistribution, pharmacokinetics, and pharmacological properties need to be clarified. (b) Long term cytotoxicity effects must be studied. (c) Eliminate the inflammatory and some polymer coatings immune response triggered by (d) Economics [23-30]. It is of crucial need to identify the exact GNP's physicochemical properties that permit optimum gastrointestinal absorption and accumulation in the site of action after oral intake and these properties are greatly determined by surface charge and size of GNPs. In the study intra-oesophageal administration of radiolabelled positive surface charges, GNPs of 2.8 nm size and negative surface charge GNPs with different sizes range 1.4 to 200 nm into healthy adult female rats. After one day and by gamma spectroscopy the amount of the GNPs in organs and tissues was determined [31-35].

Individual designs have been developed based on the nature of the tissues and human cells targeted in the treatment because the size of the nanoparticles has determined the highest values of accumulation and the load granted by the drugs. The highest accumulation of secondary organs in the human body occurred in the size of the AuNPs (GNPs) at 1.4 nm that charged with a more positive charge Of the negative charge, compared with 18 nm particles, which showed the highest accumulating values in the heart and brain cells [36-40].

GOLD NANOPARTICLES

Gold particles are ranged from large size particles to small nanparticles , they are differ in their physical properties like color , size , state of matter and activity. As well as gold nanoparticles differ from each other by shape and cluster to give a lot of characteristic shapes. The shape of gold nanoparticles affect their optical properties therefore, triangular nanoparticles have attractive optical properties in contrast to other shapes (Figure 1) [41].

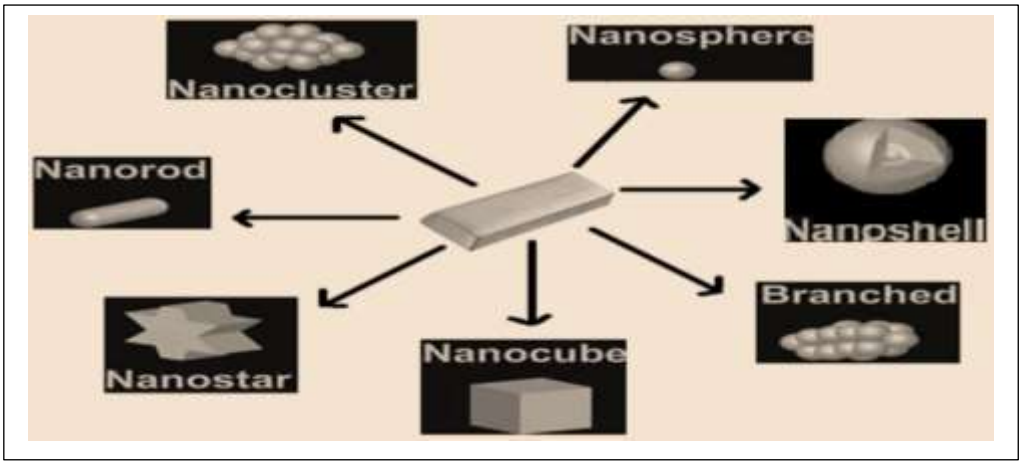


Figure 1: Various shapes of gold nanoparticles

Using of plant extract is important to purify gold nanoparticles and determine their medical applications. They are therapeuticall used to target anticancer medication to tumor cells to kill them by hyperthermal treatment as well as used for biomolecular ultrasensitive detection. Florescent nanoparticles applied to make imaging of certain enzymes and metabolite inside cancer cells .gold nanorods have a lot of applications in in the field of biosensing, photo thermal therapy and gene delivery because of their absorptive properties in the visible and near infrared region [42-46].

Gold nanoparticles highly used in CT imaging as molecular probes rather than iodine due to its higher absorption coefficient attributed to higher atomic number and electron density [47,48]. The biological safety and large surface area of gold nanoparticles are other beneficial properties of them to be used in biomedical purposes. Colloidal nanoparticles are very small in size like that of DNA and proteins and easily prepared, therefore highly used to target cells and tissues due to easy of the entrance to inside these cells. Gold nanoparticles can be used as vaccine carriers and mainly epidermal DNA vaccine delivery by gene gun gold nanoparticles due to safety and binding to various organic molecules. by coating nanoparticles with temperature labile polymer, they can be used as drug carriers [49-55].

SYNTHESIS STRATEGIES

A number of methods have been used in chemical, physical, and biological methods in synthesis and stability strategies for golden nanoparticles GNPs.

3.1. The chemical reduction method

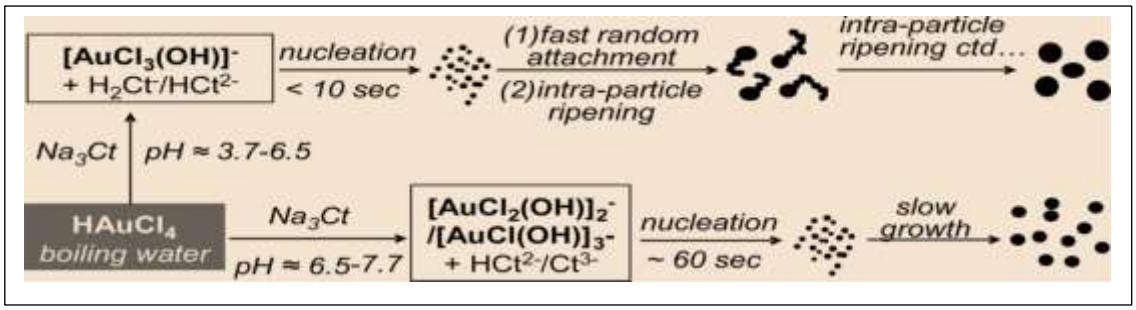
The preparation of GNPs by the chemical reduction method consist of two steps: (a) reduction step by use agents like formaldehyde, hydroxylamine, sugars, carbon monoxide, hydrogen peroxide, sulphites, acetylene, hydrogen; citric and oxalic acids (b) stabilization step by using agents like sulphur ligands, phosphorus ligands, polymers and surfactants. To avoid the aggregation of the GNP [56-60].

3.2. The Green methods

Green chemistry synthesis routes are environment friendly and non-toxic. A facile green biosynthesis method for the preparation of gold nanoparticles of size 25 + 7 nm was reported by using natural biomaterial egg shell membrane (ESM) [61-69]. In this method ESM was immersed in aqueous solution of HAuCl4 without using any reductant. Another green synthetic approach was developed to synthesized gold sononanoparticles of size 5 - 17 nm by using high-power ultrasounds and sodium dehydrate. Gold nanoparticles were successfully synthesized by adopting sun light irradiation method and were modified with folic acid and capped by 6-mercaptopurine. In this method solar energy was used to reduce the gold salt. A new green chemistry method for the preparation of gold nanoparticles has been reported, in which gold nanoparticles were formed in aqueous NaCl solution from the bulk gold substrate by natural chitosan without using any external stabilizer and reductant [70]. Gold nanoparticles of size 15 - 80 nm are also synthesized via another green synthetic route. In this method $HAuC_{l4}$ was reduced by using citrus fruits juice extracts [*Citrus limon, Citrus reticulate* and *Citrus sinensis*]. Edible mushroom was also used for the synthesis of gold nanoparticles via sunlight exposure [71,72].

3.3. The Citrate reduction (Turkevich method)

The most common method for synthesis gold nanoparticles AuNPs is the Turkevich reductive method, although there are many other methods. The Turkevich method was discovered in 1951, and some modifications were made to the methods of its construction by the scientist Frens' group, where this process of formation includes reducing citrate with gold particles to produce nanoparticles with a size of 20 nanometers. Particles with sizes ranging from 16 to 147 nanometers can be produced by adjusting the proportions of the ester components with gold. The mechanics of this method were examined by Peng's group in 2007(Schematic 1) [73-81].

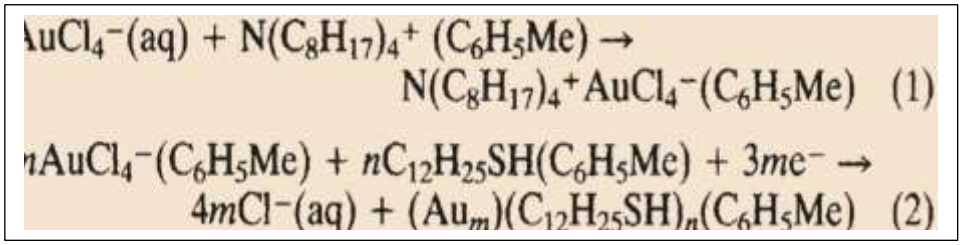


Schematic 1: shown of Two Pathways for the formulation of gold nanocrystals by citrate reduction[82]

The nucleation process followed in the synthesis of nanoparticles AuNPs can be constructed in two ways, either by reducing citrate or by determining pH values. Any of these methods can be accomplished in three Pathways, smoothing the nanowires to dots, random attachment to polycrystalline nanowires, and naming nucleation. pH values may give the most common nucleation shift pathway information [83-85].

3.4. The Brust-Schiffrin method

The Brust – Schiffirin reaction pathway involves building thermally stable, air-stable nanoparticles AuNPs with reduced dispersion values. This method was discovered by the scientist Brust–Schiffirin and his group in 1994, through which the size of nanoparticles with a range of 1.5 nm to 2.5 can be controlled. In this way, two reaction pathways were used to obtain an effective surface reaction during the development and growth process. $AuCl^{-}_{4}$ has been transformed from its aqueous solution to another organic solvent, which is staining with the aid of a phase transfer reagent, followed by a reductive pathway with sodium borohydride and dodecanethiol that shown in scheme 2. In comparison with the method of reducing the citrate, this method includes the formation of a hydrophobic mineral group and then its dissolution without a change in the properties of the formed particles. The method of Brust-Schiffirin has become more extensive when using p-ercaptophenol which provides greater stability than other pathways [86-89].



Scheme 2: Shows the Reaction for Brust–Schifrin method [82].

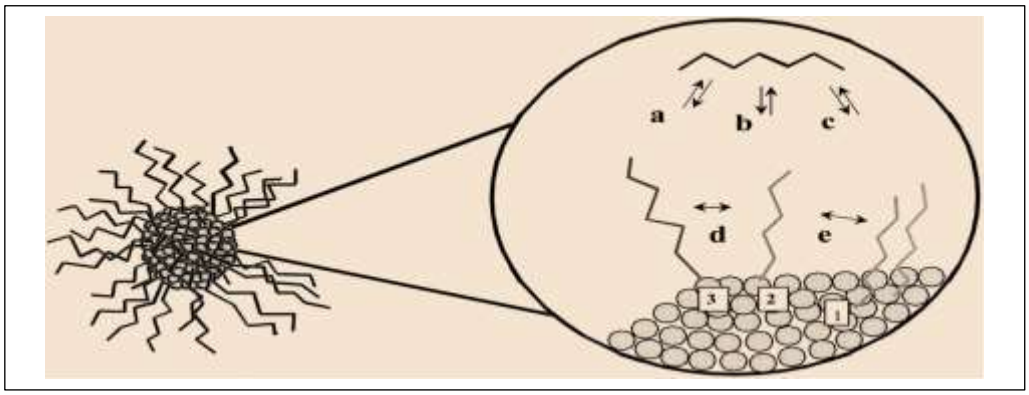


Fig. 2: Shows of the proposed processes contributory in ligand Replacement reaction on Au-MPCs[82].

The gold nanoparticles have become more stable by a proposed set of functional lecandes. Several modifications have occurred in a practiced method, and Murray's group has discovered protection for gold particles by monolayer-protected gold clusters (MPCs) as a multifunctional chemical reactor that has been widely used and gives encouraging results. The alkanethiol ligands (RS) have been used through Replacement reactions (Figure 2) [90-93].

3.5. Polymer-based synthesis of GNP

Size and shape of GNP consider a vital part in colloidal gold preparation. The interaction of polymers with GNP greatly affect the size diversity and stability of particles. Study

overcome this condition by using antitumor drug entrained into a PEG capping layer with an acid-labile spacer. According to this stated records, such a system will considerably increase the efficiency of both release and intracellular uptake of cytotoxic drug [94-98].

3.6. The Physical method

3.6.1. The Electrochemical method

The GNPs were prepared electrochemically using a simple two-electrode cell, with reduction of the cathode and oxidation of the anode. The electrochemical construction of nanoparticles was first considered by Reetz, in 1994. This procedure has been considered to be superior to other techniques of nanoparticle formation, due to its lower processing temperature, low cost, high quality, modest equipment and ease of process managing [99-102].

3.6.2. The Seeding growth method

According to this method of preparation, GNP of diameters 5-40 nm with a narrow dispersity in size were prepared. Particle size can be well ordered by change ratio of seed to metal salt. This method has the gain of being an easy, quick, and low cost; whereas the used of trisodium citrate as a source of OH ions in the seeding step and sodium borohydrate ($NaBH_4$) as a reductant [103-106].

3.6.3. Ultraviolet-induced photochemical synthesis of GNPs

The potential chemistry attributed to the use of GNPs in magnetic devices, photocatalysis, fabrication and aerosol is powerfully influence by controlling morphology and dimension features of the prepared nanoparticle. As many researches have stated, the photoreduction process permits the preparation of single crystallite GNPs. The preparation of GNPs with controllable size was effectively achieved by photochemistry [107-110].

3.6.4. Ultrasound aided synthesis of GNP

Generator of ultrasound wave was used for a water bath with controlled temperature for the ultrasonic-aided reduction of gold precursor in presence of 2-propanol. Various stabilizers have been used during this preparation method, such as citrate, disulphide and several dendrimers, for reproducibility and tunability reasons [111-114].

3.6.5. Laser ablation synthesis of GNP

Accurate and reproducible outcomes have been obtained by laser ablation procedure, in terms of shape and size attributes. So, the pulsed laser process which needs simultaneous evaporation and condensation occurrences for gold represents a comprehensive physical method that can be effectively apply to yield GNPs with tuneable properties.The preparation needs reduction of $HAuCl_4$ by laser beam of a 532 nm wavelength, producing GNPs with 5 nm and lower in size. In this method, solution of sodium dodecyl sulphate (SDS) has been consider as a model and study the effect of both laser and concentrations on the size and shape of the prepared GNPs. GNPs got by this method useful in immunochromatographic assay labelling [115-118].

3.7. The Biological method

By this method GNP are prepared by microorganisms, enzymes, and plants.

3.8. The Microbial synthesis of GNP

The necessity of eco -friendly and low cost preparation of GNPs by utilize microorganisms are highlighted due to no dangerous by-products. The process has been assumed that enzymes like ligninases, laccases and reductases are used in nucleation and growth of GNPs. Numerous factors affect the preparation and stability of GNPs like substrate concentration, pH, temperature, and static condition. Nevertheless, there are many works on enhancing these procedures. Some state that Klebsiella pneumonia mediated synthesis of GNPs and synergetic effect of antimicrobial activity to many bacterial pathogen S. aureus, E. coli, S. Epidermidis and P. aeruginosa. Other colloidal gold mediated synthesis is soil isolation of fungus Penicillium crustosum used in success whole preparation of GNPs mediated by extracellular proteins [119-123].

3.9. Plant mediated synthesis of colloidal gold

Lately, the use of plants for the preparation of GNP reflect area of concern, because of their low cost, availability, non-toxic nature and eco-friendliness. In latest years, the synthesis of GNPs using different plants such as, Aloe vera, Cinnamomum camphora, Azadirachta indica and Coriandrum sativum have been stated [124-126].

FUNCTIONALIZATION OF GNPs

Surface biofunctionalization is one of the most encouraging features of GNPs in the biomedical field and can be modified with different biomolecules, such as antibodies, peptides, and DNA. There are two types of functionalization interactions. One of them is noncovalent interactions, the other is covalent interactions. Noncovalent alterations take place through hydrophobic entrapment, electrostatic interactions, and van der Walls forces [127-130]. The binding is not solid enough to produce stable surfaces tolerate the required incubation conditions and washing steps, particularly in biological researches. Thus, the impact of the surrounding medium's pH and ionic strength is important to consider. In contrast, covalent modifications, which make use of linker molecules or immediate chemical attachment, gives more reproducibility and stability. Covalent interaction is able to tolerate a high salt concentration and is very stable under thermal settings. However, covalent interaction is more complicated, from time to time needing concentrated preparation effort on the ligands. The simplicity of this surface modification by noncovalent and covalent modifications can be used in bio-diagnostic and biosensing and for specific biological targeting [131-134].

THE BOOST OF GNPs

The drug delivery function of GNPs can be enhanced in two ways, one way by prolongation of their plasma half-life and therefore accumulation within cells and the other way by increasing cellular uptake and drug release inside targeted cells. polyethylene glycol conjugation with GNPs will decrease their clearance by macrophages and reticuloendothelial system (RES) [135-138]. Because it provides a steric barrier against macrophages as well as to potentiate penetration and retention process. Zwitterions could be used also for the same purpose because it is neutral and therefore, prevent interaction with macromolecules of cells like receptors and proteins. Conjugation with ligands like folate, peptides or antibodies will provide better targeting of GNPs to cancerous tissues by binding to specific receptors on diseased cells [139-142].

Size is also an important factor that determines the half-life of GNPs since large particles are more rapidly cleared by macrophages and RES, although the ideal size for cellular uptake till now it is unknown. Wong et al. founded an inverse relationship between size and cellular uptake in contrast to Yue et al. who founded that larger size GNPs have higher cellular uptake than smaller ones. Kumar et al. concluded the same findings as with Wong et al [143-145].

Morphology of GNPs is another critical factor that affects the cellular uptake, studies found that spherical GNPs have a higher rate and extent of cellular uptake than rod-shaped ones. Xie et al. found that triangular GNPs have higher cellular uptake than star and rods shaped ones. Surface charge of GNPs is another important factor in addition to size and shape that determine the rate of cellular uptake, highly positive GNPs are more efficient in cellular uptake than negatively charged one since cells are negatively charged. Studies found that bovine serum albumin and installed glucose could be used as ligands on GNPs surface to enhance binding to specific tissue receptors and thus increase uptake. pH and temperature are critical factors that affect drug release in diseased tissues so acidic pH around cancer cells determine the release of drug by using PH responsive formulations and heat-sensitive materials that control drug release. Another example is by using glutathione responsive materials with GNPs to enhance the release of drugs inside cancer cells since they are rich in glutathione [146-148].

APPLICATIONS OF NANOPARTICLES

The gold nanoparticles GNPs (AuNPs) have unique properties due to their electrical and magnetic advantages. A large number of studies concerned with studying AuNPs molecules in biomarking, chemical sensing, human biological medicine, electronic phototherapy, thermal phototherapy, nanotechnology medical imaging, DNA diagnosis of both types, treatment transfer techniques, study of transfer and attribution of reagents to AuNPs particles in the treatment of cancers (Table 1) [149-151]. Various sensors based on the action of the reagents assigned to the AuNPs particles based on the principle of the color change of the detector can identify and estimate the various metal ions. The detection paths were used by the sensor method to determine the ions of lead, mercury, copper and zinc in the water. Inert elements such as gold play an active role in the work of the sensors, due to the ratio of the total area of the gold particles to their size. Biomolecules assigned to the nanoparticles have been used in the work of medical biomedical devices such as MPA (Mercaptopropionic Acid) assigned to AuNPs. The linear range of the sensors ranges from 0.25 mM to 1.25 mM at a concentration of 0.025 mM glucose [152](Figure 4). The work of LSPR biosensors is based on the surface plasmon resonance of the gold nanoparticles, and catalixar derivatives have been used for the purpose of enhancing the efficiency of the work with the gold nanoscale sensors. DNA has been detected using peptides in the nanosensors and has proven highly efficient in identifying the amino acids and quaternary ammonium ions and prenium as well. The anandium tin oxide electrode used with the TiO_2 compound based on AuNPS particles was used to estimate the catechol (CC) and hydroquinone (HQ) with the help of volumetric pathways. Catechol was estimated in tea extract using this method [153-155].

Table 1: Shapes of gold nanoparticles and their applications

Shape	Size	Application
Nano rod	2-5 nm	Drug delivery and photothermal therapy [15].
Hollow particle	25 nm	Photo-electronics, catalysis and cancer therapy [12]
Triangular particle	3.85-7.13 nm	Highly effective against *E. coli* and *K.* pneumonia [23]
Faceted particle	50-100 nm	Effective, reproducible, and stable large area substrates for NIR SERS [near infra-red surface enhanced Raman spectroscopy] [25]
Nanocube	50 nm	Field enhancement applications and refractive-index sensing [28]
Nanocage	50 nm	Effective molecular contrast agent for nonlinear endomicroscopy imaging [19] and in vivo medical applications [29]
Nanobelt	Thickness, ~80 nm, Width, ~ 20 μm, Length, ~0.15 m.	Strain sensors
Branched particle	90 nm	Substrates for SERS-based imaging of kidney cells [30]

6.1. Surface plasmon resonance (SPR)

The optical properties of gold nanostructures are influenced by surface plasmon resonance (SPR). Plasmon resonance is the electronic frequency that occurs on the surface of gold nanoparticles when its frequency coincides with that of the magnetic wave. Therefore, the area of nanoparticles plays an effective role in the effect of plasmon resonance(SPR) [156-158].

6.2. Sensor material

AuNPs have photovoltaic properties that make them very suitable for chemical sensing, and the inactivity properties of these particles make them biomedical materials of very low toxicity compared to some biocompatible technological polymers [159-162].

6.3. Nucleotides sensor for homogeneous detection

In 1997, the discovery of the ability of AuNPs to modify the surface of nanoparticles using threatened nucleotides, its study of stability and hydrobiological degree. This discovery paves the way for finding highly sensitive and selective materials that make building nanoparticles of gold more stable, cooperative and highly corrosive in stimulating surface interaction [163-165]. Figure 3 shows the result of a reaction of a mixture of DNA-AuNPs to form a polymeric network, accompanied by changes in color for this reaction from red to purple. This change is governed by differences in the size of the assembly and the optical properties of the particles. Also, the intense color of the particles of AuNPs is due to SPRs and hence the gold nanoparticles appear Formed with a size of 13 nm and a red color. Surface plasmon show relatively narrow absorption values at the wavelength of 520 nm, with an ultraviolet spectrum, while some AuNPs show a purple color at a range of absorption values of 520 to 574 nm. This means a red displacement in the AuNPs [166-168]. The greatest importance lies in discovering the DNA to collect the AuNPs as a lining on the DNA, and this way to discover the DNA is much better than the traditional methods based on fluoridation, but there are some bad advantages from using color strategies in detection because they have a specific detection limit, especially when using concentrations. The picomular was reduced to the concentration of the nanomolar due to the limited sensitivity of this process, but low detection limits can be avoided and modified when using low-enriched nucleotides by dithiane epidrosterone functionalized oligonucleotides [169-172].

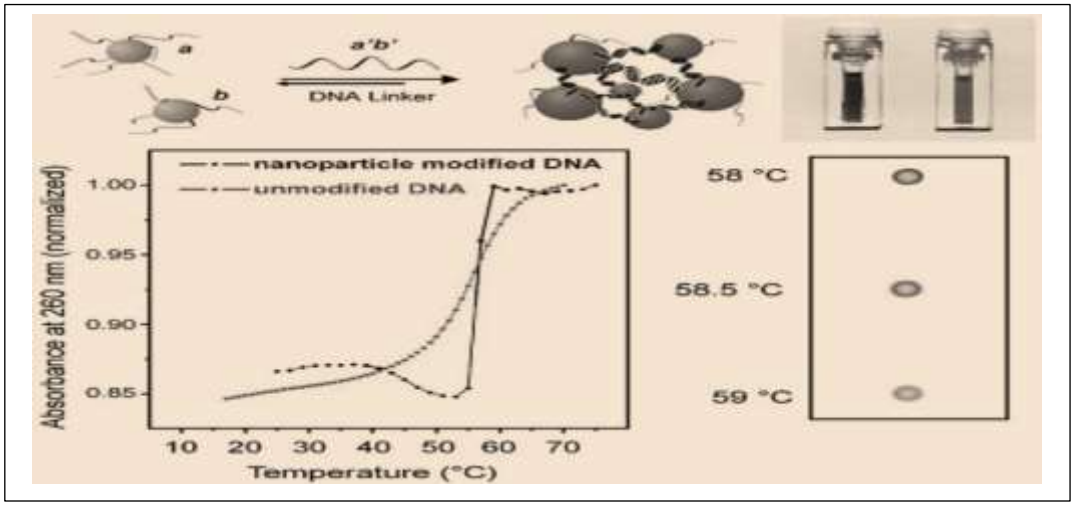


Fig. 3: shows the Properties of DNA-functionalized AuNPs [82].

6.4. Nucleotides sensor for heterogeneous detection

High sensitivity techniques have been developed to detect DNA and RNA strings in the same in the same test sample. This codification has been used by Letsinger and his group by a sandwich containing fixed capture. Through the high concentrations of the target sequence, the antibody antibody attached to the surface of the nanoparticles can be observed with the naked eye, and if low concentrations are used this will enhance the silver shells that will increase the size of the AuNPs to the micrometer and thus facilitate its detection process. The Letsinger method is 100 times more sensitive than traditional Fluorescence methods [173-175]. Human RNA samples have been used to detect mRNA matrices, and with the development of other tests, new methods have been worked out that are more sensitive to measurement. AuNPs of different sizes can be used at the same time to detect the target sequence with a dual- color reading(Figure 4) [176-178].

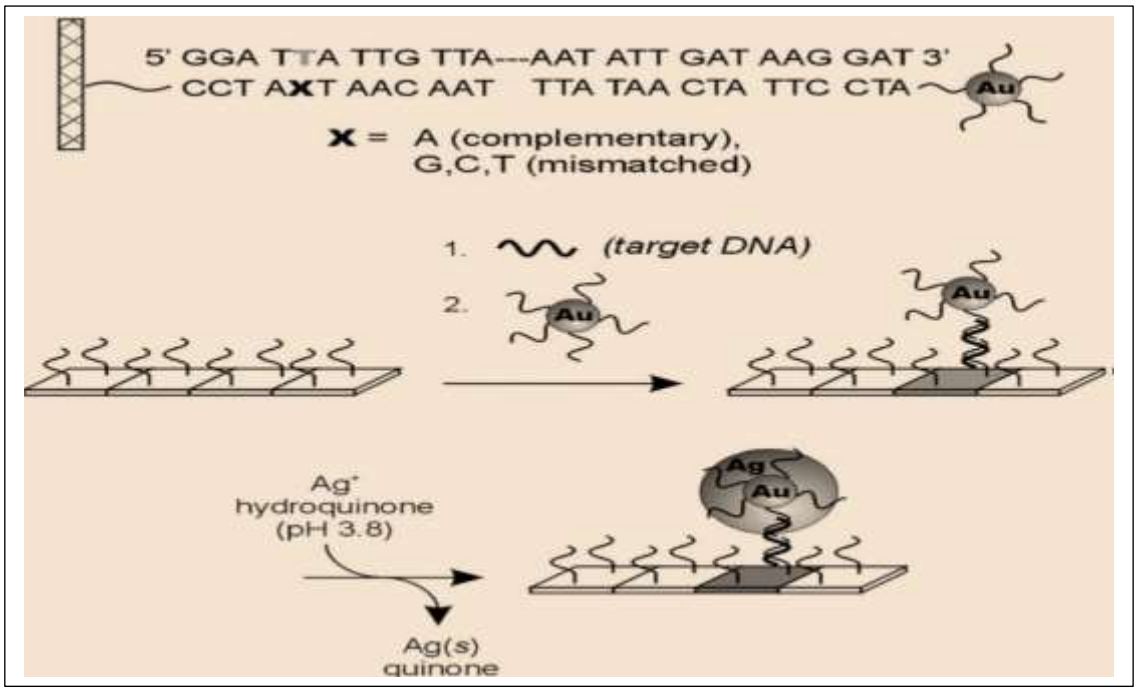
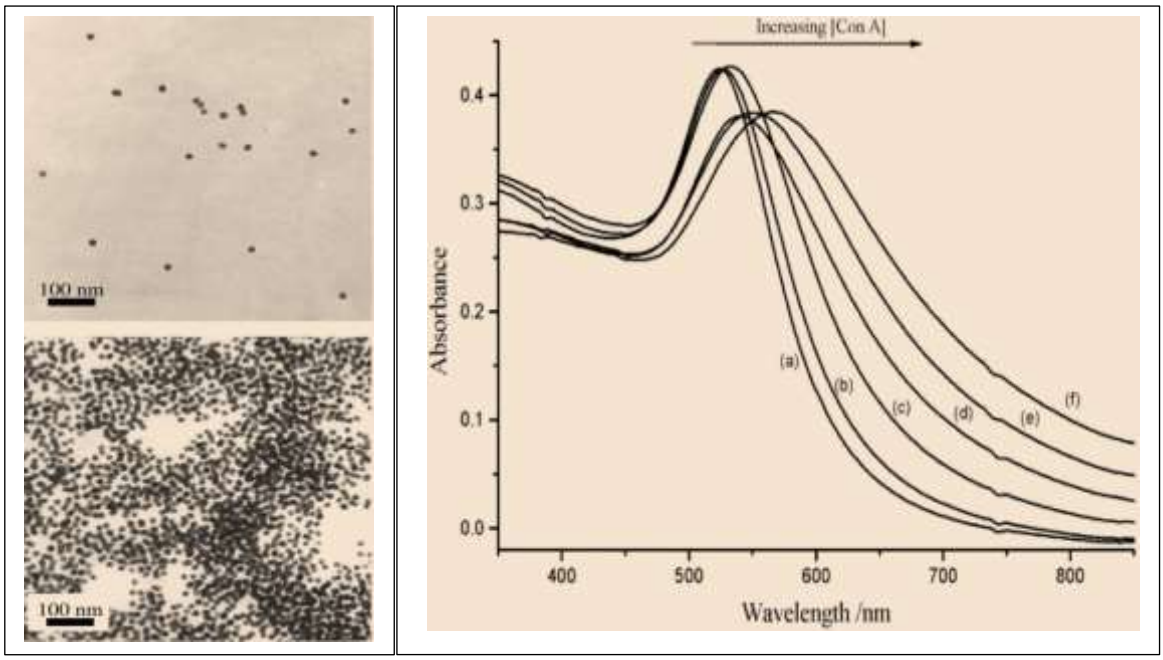


Fig 4: shows of scanometric of DNA detection assay [82].

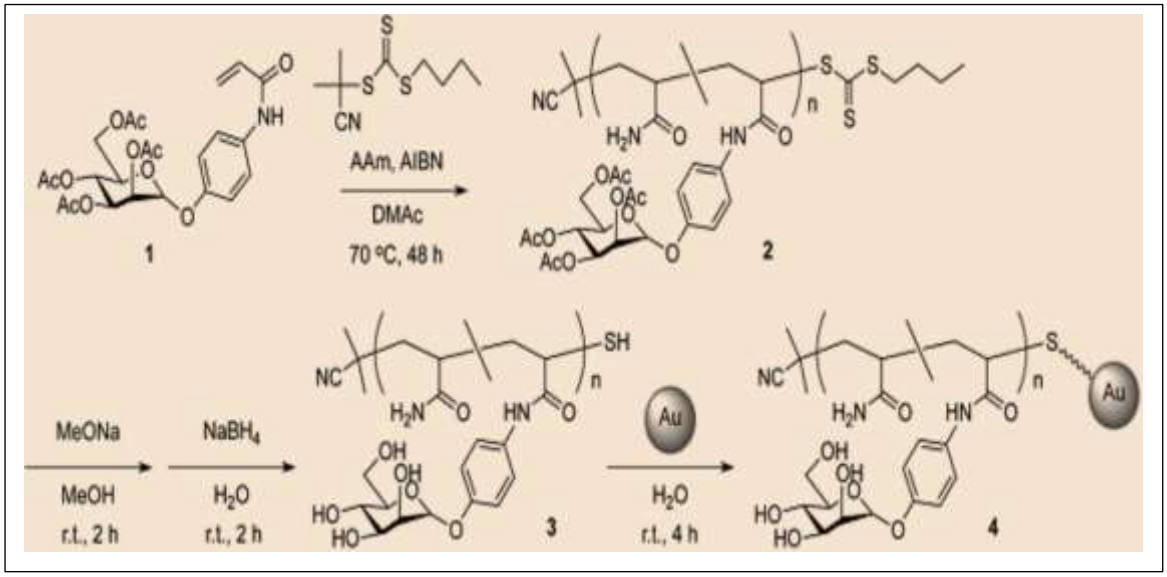
6.5. Protein sensor

The color change from red to violet resulting from dispersion can be considered as well as the use of AuNPs aggregation in color sensors to detect DNA and RNA. It can also hybridize DNA. A number of studies have demonstrated the use of lectin-sugar in sensing sugar when an interaction between sugars and lectin occurs and that this reaction is appropriate for biological sensing. Russells and his group studies have shown that the stable AuNPs of mannose sugar can be used to detect lectin (Figure 5) [179-182]. The interaction between sugar monomers, which are weak and thus the sensitivity of the sensor, decreases when using a polymerase chain reaction chain reaction (RAFT) reaction pathways because preparation in this way provides functional groups ending with the triol group, which can correspond to the surface area of the gold particles to make AuNPs. Scheme 3 illustrates the stages of constructing polyacrylamide associated with mannose sugar using the RAFT polymerization method. Reducing the thiocarbon functional group to a reducing group is thiol, through which mannose sugar is combined with the gold surface that contributes as stabilizers to prevent the aggregation of AuNPs. Genetically modified bacteria introduced into the polymer have the ability to form strong bonds with protein because of the many bonds that are affected with protein. The RAFT technique was used to polymerize the modified acrylamide with glucose sugar which showed a clear association with the surface of AuNPs (Scheme 4) [183-185]. The complexes prepared to detect the blood components did not show any interaction between the red blood cells and thus show their ability in biological biological applications. The highest importance is shown in the use of glucosamine prepared in protein sensors (Scheme 5) [186]. Regardless of the studies, glucose-polymer binding with Concanavalin A was demonstrated by a multi-component bonding. Sugars can be used as terminal modifiers instead of as peripheral monomers (Scheme 6) [187]. The linked lectin, which is assigned to the AuNPs particles, was used to detect the sugars. Once the lectin was linked with the glucose sugar, it would change the color of the glucose to red due to the assembly process and thus the detection speed and stability of the AuNPs particles with the glucose could be adjusted and a polymeric coating was obtained to reach the optimal detection state [188-190].

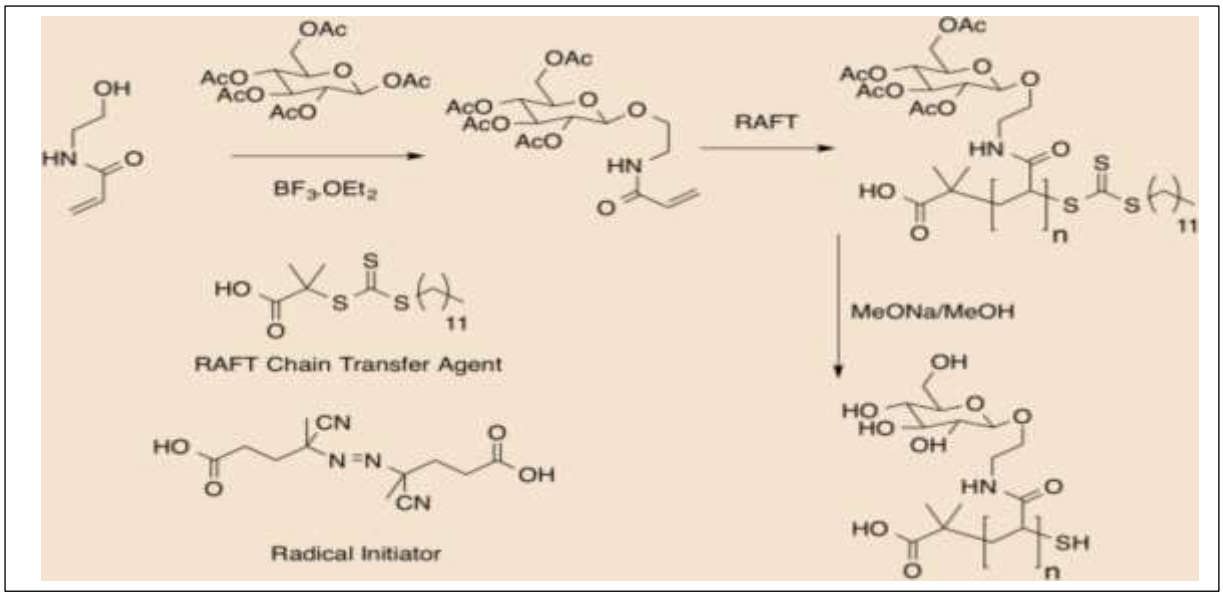


(a) (b)

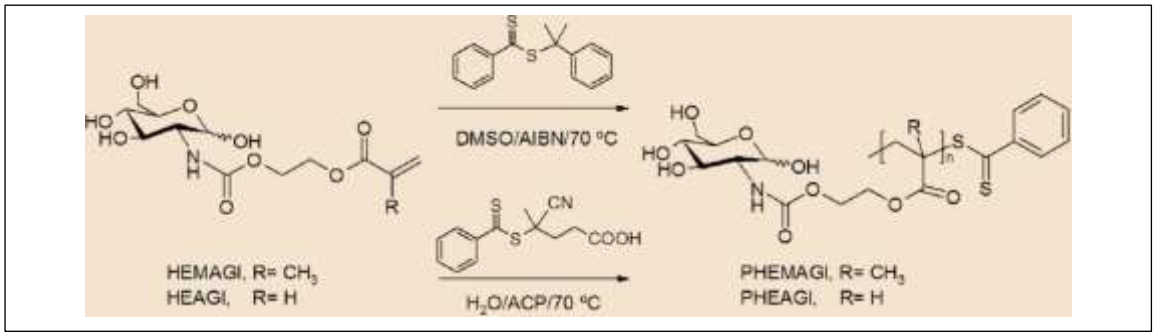
Fig. 5: (a) shows that the mannose stabilized with AuNPs (b) Changes in UV-Vis spectra for the mannose stabilized with AuNPs



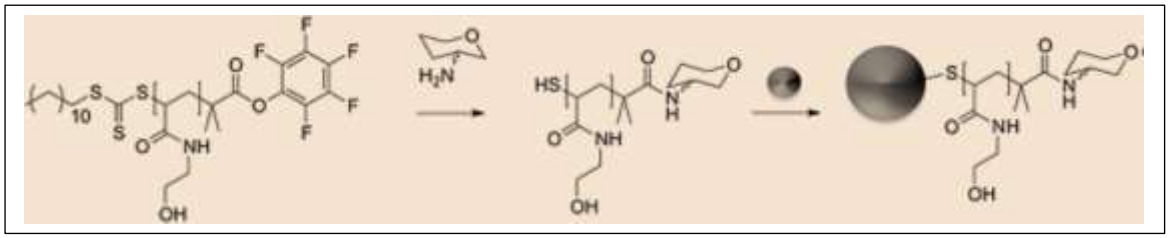
Scheme 3: shows the Synthesis of the glycopolymer and the preparation of the polymer-immobilized AuNPs



Scheme 4: shows the Synthesis of poly(ß-D-1-glucopyranosyl hydroxyethyl acrylamide) [82].



Scheme 5: Shows the Synthesis of glucosamine functionalized polymethacrylate



Scheme 6: Shows the Synthesis of polymer-stabilized AuNPs [82].

6.6. Common drugs for cancer Therapy

Constructive pathways for clinical treatment of cancer are confined. Surgical restriction, chemotherapy and irradiation are some common tactics used for cancer therapy but these approaches are not only toxic, non-specific but also cause various side effects [191-193]. Cancer patients undergoing radio and chemotherapy face drug resistance such as cisplatin, cancer related fatigue (CRF) and several cardio vascular effects such as cardiomyopathy, ischemia, arrhythmias, hyper tension, thromboembolism, pericardial diseases or heart attack as they damage the cancer cells along with the destruction of healthy cells [194-196].

Besides of some conventional approaches, chemotherapy remains the primary treatment for cancer but it is not much restorative because of various side effects caused by unspecified drug distribution in the body due to several chemotherapeutic agents such as cytotoxic drugs [197-199]. Paclitaxel (PTX) shows cytotoxicity against different types of cancer so it is considered to be an essential chemotherapeutic drug with limited therapeutic effects due to toxicity caused by poor water solubility and selectivity. Because of these shortcomings, effective approaches should be considered.

Chemotherapeutic agents cause various side effects in cancer patients such as nephrotoxicity, vomiting, myelosuppression, severe nausea, ototoxicity and neurotoxicity due to CDDP (cisplatin) administration whereas gastro intestinal disturbances, acute nausea, vomiting, stomatitis, alopecia baldness, neurologic disturbances, bone marrow, aplasia, cumulative cardio toxicity and bone marrow depressant effects due to doxorubicin administration [202,204].

Due to fluoropyrimidines (5FU), methotrexate, irinotecan and cisplatin patient may suffer from adverse diarrhea and constipation [205]. When treated with temsirolimus as a single drug anemia, hyperglycemia, stomatitis, hypophosphatemia, interstitial lung disease and pneumonia were reported in patients suffering from advanced renal cell carcinoma [206]. Each year, large numbers of deaths are caused by cancer because lack of selectivity, drug targeting ability, inefficient metastatic tumor therapy and drug resistant tumor cells (Table 2). Therefore advanced chemotherapic treatments have been needed to kill cancerous cells [207]. Today in order to avoid side effects fuscous of scientists are shifted towards natural products which still needs to prove their effectiveness [208].

Table 2: Conventional intravenously administered drugs and their side effects

Chemotherapeutic agent	Cancer type	Possible short-term side effect
Carboplatin (Paraplatin)	Cancers of the ovary, head and neck, and lungs	Decrease in blood cell counts, hair loss (reversible), confusion, nausea, vomiting, and/ordiarrhea
Cisplatin (Platinol, Platinol-AQ)	Cancers of the bladder, ovary, and testicles	Decrease in blood cell counts, allergic reaction, including a rash and/or labored breathing, nausea and vomiting that usually occurs for 24 hours or longer, ringing in ears and hearing loss, fluctuations in blood electrolytes, and kidney damage
Doxorubicin (Adriamycin)	Breast cancer, lymphoma, and multiplemyeloma	Decrease in blood cell counts, mouth ulcers, hair loss (reversible), nausea and vomiting, and heart damage
Paclitaxel (Taxol)	Cancers of the breast, ovary, and lung	Decrease in blood cell counts, allergic reaction, nausea and vomiting, loss of appetite, change in taste, thin or brittle hair, joint pain (short term), and numbness or tingling in fingers or toes
Fluorouracil (5-FU)	Cancers of the colon, breast, stomach, and head and neck	Decrease in blood cell counts, diarrhea, mouth ulcers, photosensitivity, and dry skin

6.7. GNP conjugated Antibiotics Drug Delivery System

In vitro evaluation of GNPs conjugated antibiotics shows significant reduction in minimum inhibitory concentration for streptomycin and kanamycin conjugated GNPs and slight decrement in GNPs conjugated ampicillin minimum inhibitory concentration value compared to its free drug form. In addition to improvement in heat stability for all studied antibiotics values in their GNPs conjugated form, this formulation provides a modern, safe, and effective strategy for the treatment of bacterial infections with GNPs conjugated drug delivery syste [209-212]. New approach utilizing bacterial toxins to specifically deliver antimicrobials drugs to the sites of infections and activation of smart drug release from GNPs. Coupling of chitosan functionalized GNPs to the liposomes surface lead to increase liposomes stability and prevent immature drug release in physiological environments or labeled storage condition. Nevertheless, once bacterial the stabilized liposomes toxin secreted these protected liposomes find bacteria, the toxins will penetrate liposome membranes and generate pores, through which the antibiotic drug released. The released antibiotic subsequently exerts its antimicrobial effects on the toxin-secreting bacteria as a smart drug delivery system [213,216]. In this study vancomycin used as a model bactericidal dug to methicillin-resistant staphylococcus aureus (anti-MRSA) by using GNP-Liposomes nanocarriers, result shows that the encapsulated vancomycin prepared as GNP-liposomes can entirely release within 24 h in response MRSA bacteria toxin and inhibit MRSA growth. Other work study GNP conjugated antibiotic (ampicillin, streptomycin and kanamycin) as drug candidate for this drug delivery system. Where bactericidal efficacy evaluated in different bacterial strains Staphylococcus aureus, Escherichia coli and Micrococcus luteus and find there is more significant reduction in minimal inhibitory concentration with greater bactericidal activity. In addition, all these GNPs conjugated antibiotics revealed higher storage condition stability (heat and UV) in comparison to their free forms [217-219].

6.8. GNP and gene delivery systems

Gold nanoparticles have been used as an alternative delivery system for many drugs, proteins, RNAs (siRNAs), plasmid DNAs (pDNAs), peptide and chemotherapy. Surface modification systems for functional genes assigned to GNPs, such as adding thiol, amine and carboxyl groups, have been modified. The modification can be made by adding positive polymers. The GNP-RNA nanoscale system has been widely used in siRNA connection. The siRNA synthesis was changed by adding a thiol group to improve the efficacy of GNPs. The modified siRNA synthesis with thiol showed strong adsorption on the surface of GNPS particles within human cells, directing the SERNA group directly and the cause of RNA interactions with the reductive cell cytoplasm

unlike the direct association with the surface of GNPs particles. Binding of siRNA ends to chemical bonds with GNPs particles attached to the polymers. This binding by reducing bonds leads to the formation of a fissionable environment and the formation of smart siRNA in the cytoplasm in the cell. This work depends on the control factor of pH values [220-222].

The induction of target protein synthesis was initiated by the plasmid DNA delivery vectors (pDNAs), whether the delivery systems used are viral or non-viral, these conductive systems are characterized by high efficiency in the transmission of infection and this is the main reason for their repeated uses, despite the limited efficiency of the non-viral delivery system However, it can be a substitute for viral delivery systems due to the possibility of modifying the design of non-viral delivery systems, in addition to that, the small size of GNPs particles are highly efficient in transporting very high payloads for each individual GNP carrier due to this The largest surface area of a particle to a ratio of volume [223-225].

6.9. GNPs Recent Advances in Vaccines

In 1928, the scientist Cole and his group discovered the ability of the immune system to respond to cancerous tumors, as stated in his study that vaccination with stimulating cancer cells can increase the degree of immune response against tumors, thus finding vaccines against cancers. The high selectivity of these vaccines makes them useful as a treatment for the destruction of cancerous tumor cells. Mankind is very acceptable. Studies concerned with the localization of antigens associated with cancerous tumors (TAAS) and tumor-specific antigens (TSAS), and efforts have been combined to develop approaches for these studies. It includes an immunization method against tumors by nature of tumor cells and genetically engineered tumor cells engineering [226-228].

All vaccination studies aim at working with vaccination strategies and improving immune response and developing them to be able to destroy cancer cells only without other natural cells without damage. Gold nanoparticles have proven their ability to visualize the delivery of effective antigens to cancer cells and have helped stimulate the work of T-lymphocyte during effective chemotherapy. Nanoparticles of 15 to 50 nm are very effective in delivering these antigens against more than 45 pathogens of parasite, bacterial and viral infections [229-231].

Various forms of nanoparticles of gold and of different sizes have been used as an antigen holder in oncology treatments in general by pairing with the targeted physico-chemical antigen. Extensive studies were conducted on the role of the SH group in protein molecules and their association with gold nanoparticles. GNPs are also coupled with a multi-sugar-bond or protein link before being antigen-loaded. The latest engineering designs have been used to make GNPs suitable for loading vaccines and antigens by improving the shape, size and surface characteristics. These modern designs have also contributed to making nanoparticles suitable for improving immunity and proliferation in the lymph nodes and activating T-cell response to the antigen [232-234].

6.10. Gold nanoparticles for improved and enhanced phototherapy.

The therapeutic techniques of gold nanoparticles are divided into four main sections that work as an anti-cancer treatment, which is PTT photodynamic and dynamic radiotherapy. The main function of these particles is dynamic photodynamic therapy PDT and photothermal therapy PTT. The PDT technology is non-invasive and works using light-sensitive agents (Optical Optimizer) as this technique works to produce reactive oxygen in different types (ROS) for the purpose of damaging target cancer cells, as it uses hydrophobic photocatalysts such as phthalocyanin and porphyrins, and thus it needs a PEGylated nanocomputer for the purpose of improving complete dissolution in water, and the PDT provides an effective protection system (5 -fluorouracil) when coupled with .GNPs, the GNPs provide an effective carrier and carrier for treatment to divorce the payload on the ultraviolet with a maximum wavelength. The function of PTT is a preventive measure to destroy cancer cells at high temperatures in GNPs when irradiated by light. GNPs have the ability to absorb SPR if irradiated with light using short laser waves [235-238].

PTT was coupled with GNPs for the purpose of creating a lethal pulse of cancerous cells. Using PTT and PDT with X-rays only for a specific area of cancer, and therefore the activity of using X-rays is more effective than in the infrared in the activation of PTT and PDT. When using the gold element in irradiation, which has a higher absorption coefficient and less toxicity, therefore, the killing of prostate cancer cells has been improved by about 15% - 20% when assigned to GNPs by proton radiation [239-241].

The targeting systems of GNPs particles differ in the degree of delivery of each drug according to the effects and the size and quantity of materials associated with the GNPs particles. For example, when the GNPs are in small capsules, they are sensitive to heat, especially when LSPR is used in the process of operation when medicines are released from the capsules. After destroying the nanostructures of GNPs [242-244].

6.11. Applications of targeted delivery systems from cells to clinics

Nanoscale platforms are used to diagnose different types of cancer. The target delivery system for nanoparticles acts as anti-cancer platforms such as audited liposomes, tails nanoparticles and albumin based drug carriers. Nanoparticles have been used to diagnose cancers by photogrammetry during surgery and bilateral imaging. In general, nanoscopy has become effective in early diagnosis of cancerous and human diseases. Dual contrast factors allow the diagnosis of areas of interest to be examined in two independent ways, namely MRI detectors and the use of fluorine agents. In the case of MRI, there is very high sensitivity and accuracy in diagnosis. Fluoroscopy compensates for MRI in the case of overcoming restrictions during the surgical procedure being imaging Uni-style. This study offers a wide application in the surgery of cancerous tumors in the ovaries in the early stages of the tumor, with

specific imaging of the tumor for patients suffering from ovarian cancer through folic acid receptors. Gold nanoparticle platforms are a versatile platform that provides desirable results for diagnostic systems as they are prepared in a size range from 1.5 to 10 nanometers. Usually gold nanoparticles are made using hydrogen tetrachloride and the treatment is loaded by covalent bonding. Gold nanoparticles have particularly beneficial properties in diagnosing cancers, compressible heart size, mono-bifurcation, low toxicity, light scattering properties, ease of manufacture, and the ability to bind to biomolecules via Au-S. Gold nanoparticles have demonstrated the potential of targeted heat therapy in conjunction with a chemotherapy agent in treating MDR tumors [245-247].

Heo et al. Described. (2012) golden nanoparticles as a diagnostic platform where they operate on the surface using biotin, PEG, rhodamine Bletaed beta-cyclodextrin (beta-CD) and baclitaxel. Paklitaxel is a compound that is included with beta-CD and has then been coupled with golden nanoparticles. Laboratory studies indicate that golden nanoparticles have a high tendency toward cancer cells such as MG63, A549 and HeLa compared to NIH_3T_3 cells. Golden nanoparticles have demonstrated a toxic effect on HeLa cancer cells [248-250].

Effective and smart gold nanoparticles have been developed where DOX is coupled with nanoparticles via Au-S using peptide tape bases, Cys-Pro-Leu-Gly-Leu-Alu-Ala-Ala-Gly-Gly (CPLGLAGG) where the cleavage is Specifically by protease (Figure 4) and demonstrated by animal experiments after injection of functional gold nanoparticles in tumor-bearing mice, excessive protease [251,253].

ADVANTAGES OF GOLD NANOPARTICLES

Gold nanoparticles mediated drug delivery systems have many advantages over other nanocarriers as well as to conventional drugs. Gold nanoparticles have been widely used as acancer antigen and in tumor therapies [254]. Some advantages are listed here; (i) Gold nanoparticles have unique optical [255], physical and chemical properties [256] due to their size and shape [257]; (ii) Gold nanoparticles have high surface area [258] which provide dense drug loading; (iii) These particles are biocompatible [259] and are readily available for conjugation with small biomolecules such as proteins, enzymes, carboxylic acid, DNA, and amino acids [260]; (iv) Gold nanoparticles have controlled dispersity [261]; (v) Due to small size and uniform dispersion they can easily reach to the targeted site with blood flow [262]; (vi) They are non-cytotoxic to the normal cells [263]; and (vii) Gold nanoparticles are easily synthesized by various methods [264].

Good characteristics in the using gold nanoparticles as a drug carry and delivery system

- ➢Control the ratio of the volume to the surface area of the gold nanoparticles easily to achieve the goal of their use.
- ➢Control the release and preservation of the drug during transport and storage, and achieve increased effectiveness and disposal of side effects.
- ➢Achieving the highest capacity of the particles to load and integrate the drug without any chemical reaction.
- ➢Ease of attaining the targeting sites with nanoparticle surface targeting.
- ➢The delivery of medications can be achieved with high success to the mouth, eye, nose, intravenous injection, etc.
- ➢Stability and reliability in drug delivery can be enhanced by avoiding combination of drugs and nanoparticles.
- ➢Restricting the motion of the drug particles that are supported by the surface of the AuNPs reduces drug drain.
- ➢The surface of the particles can be easily modified if they are in a solid / liquid phase.

DISADVANTAGES OF NANOPARTICLES

8.1. Potential toxicity

While the small size of nanoparticle is what makes them so useful in medicine, it is also the factor that might make them potentially dangerous to human health [265].

8.2. Environmental concerns

Artificially manufacture nanoparticles will be new to the environment in type and quantity and would constitute a new class of non biodegradable pollutants [266].

IDEAL PROPERTIES OF NANOPARTICLES

- ➢It can be used as a natural or synthetic polymer
- ➢cheap
- ➢Toxic free
- ➢Easily decomposes
- ➢It does not clot easily
- ➢It does not affect the immune system
- ➢The diameter of nanoparticles must be less than 100 nanometers
- ➢Platelet aggregation does not occur during the assignment of drugs to nanoparticles in the treatment of hematology.
- ➢The use of nanoparticles does not cause tissue infections

CONCLUSION

Gold nanoparticles have revolutionized the field of medicine because of its widespread applications in targeted drug delivery, imaging, diagnosis, and therapeutics due to their extremely small size, high surface area, stability, non-cytotoxicity, and tunable optical, physical and chemical properties. Functionalized gold nanoparticles with various biomolecules such as proteins, DNA, amino acids, and carboxylic acids have been used to provide excellent cancer therapy and provide excellent drug delivery systems. Targeted delivery and programmed release of therapeutic drugs to the specific site is achieved by using gold nanoparticles because they can bear high drug load and release it to the specific site through various administration routes and can interact with the cancerous cells. Side effects of conventional drugs have been minimized by conjugation

with gold nanoparticles and they increase the quality life of patients.

THE DISAGREEMENT OF INTEREST

The authors declare that there are no conflicts of interest.

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