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REVIEW ARTICLE

Gold Nanoparticles: An Emerging Novel Technology for Targeted Delivery System for Site-specific Diseases

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Abstract: Gold Nanoparticles (GNPs) have emerged as a novel technology in the field of targeted delivery systems, offering promising solutions for site-specific disease treatment. These nanoparticles possess unique physicochemical properties, such as controlled size, shape, and surface chemistry, which enable precise manipulation for enhanced therapeutic efficacy. The biocompatibility and ease of functionalization of GNPs facilitate the conjugation with various biomolecules, including drugs, peptides, and nucleic acids, thereby improving their targeted delivery capabilities. Recent advancements in nanotechnology have leveraged GNPs for the treatment of a range of diseases, particularly in oncology, cardiology, and neurology. In cancer therapy, GNPs can be engineered to target tumor cells selectively, minimizing damage to healthy tissues and reducing side effects. This is achieved through the conjugation of GNPs with tumor-specific ligands, antibodies, or aptamers, which direct the nanoparticles to malignant cells, allowing for localized drug release and improved therapeutic outcomes. Moreover, GNPs exhibit remarkable potential in diagnostic imaging and photothermal therapy. Their unique optical properties, such as surface plasmon resonance, enable their use as contrast agents in imaging techniques, providing high-resolution and real-time monitoring of disease progression. In photothermal therapy, GNPs convert light energy into heat, effectively destroying targeted cells with minimal invasiveness. The development of GNP-based delivery systems also addresses significant challenges in drug resistance and bioavailability. By overcoming biological barriers and enhancing cellular uptake, GNPs improve the pharmacokinetics and pharmacodynamics of therapeutic agents. However, despite these advancements, the clinical translation of GNPs faces challenges such as potential toxicity, long-term stability, and regulatory hurdles. In conclusion, gold nanoparticles represent a cutting-edge approach in targeted delivery systems, offering significant potential for site-specific disease treatment. Continued research and innovation are essential to overcome existing challenges and fully realize the clinical applications of GNPs, ultimately revolutionizing precision medicine.

Gold nanoparticles exhibit unique physicochemical and optical properties. The gold nanoparticles have advanced techniques to cure different chronic diseases. Today, gold nanoparticles are aided by photodynamic therapy and radiation therapy as drug carriers. Due to this, researchers now focus on medical sciences to treat various diseases and therapeutic applications. This review provides all the aspects of gold-based nanoparticles, methods, and their pharmacological benefits in different fields of medical sciences. We also discuss various preparation methods and their advantages in pharmaceutical formulations.

Keywords: Gold, gold nanoparticles, method of preparation, nucleic acid delivery, targeting, photothermal therapy.

1. INTRODUCTION

Researchers have done various research to develop and exploit nanotechnology-based pharmaceutical formulations or products such as micelles, inorganic nanoparticles, liposomes, niosomes, and nano lipid carriers (NLC). For a long time, despite the various up-gradation and research in medicine, cancer has still been a significant problem globally as one of the leading reasons for death, with almost 10 million deaths in 2008. In the case of cancer treatment, the site-specific and targeting site is the main focus area, but the adverse effects are the main problem, especially in chemotherapy [1].

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These nanotechnology-based pharmaceutical products have major advantages over the conventional dosage forms, such as particle size and high surface volume ratio, which help to permeate the drug through biological membranes and put up an increased focus on molecule manufacture control biotic process and their definitive chance inside the body [2].

The nano-gold-based drug delivery system is among the researcher's most focused areas. Nanoparticle systems are used on site-specific tissues to improve bioavailability and solubility, reduce side effects and toxicity, or protect therapeutic agents from degradation [3, 4].

In this review, we talk about gold nanoparticles, focus on cancer-based nano-formulations, and highlight the adverse effects and limits of conventional dosage. Lastly, we are given different examples and artworks of various potentials of site-specific treatment of tumors and various chronic diseases that exceptional properties of gold-based nanoparticles can attain.

2. OVERVIEW OF GOLD NANOPARTICLES (GNPS)

Gold discovered Gold; it originated in essays by Chinese and Indian researchers in the 5th to 4th centuries BC. Colloidal Gold has various medicinal properties and is effectively used in medicine. In the 20th century, tuberculosis and rheumatic disease treatment were used in ayurvedic preparation in India. Gold was mainly used in the 17th century; philosopher Francisco Antonii, in his book, defines the preparation and usage of colloidal Gold [5-7].

Researchers have recently focused on nanotechnology to develop various nanotechnology-based formulations for diagnosing and treating various diseases. Several nanoparticle-based drug delivery systems have proved site-specific and target brain cancers because the conventional dosage form is inadequate. Nanoparticles have unique properties for enhancing permeability and retention to accrue and interrelate with tumor cells [7]. Therefore, the interface of nanoparticles and vascular pathways is helpful in treating cardiovascular disease. Gold nanoparticles are effectively used in cancer, are non-toxic, and have fewer adverse effects [8]. Gold nanoparticles (AuNPs) have mainly been researched area the manifest advantages are easily manufactured; the size range is 1-1000 nm and they have spherical, rod-like, and cage-like shapes. It is biocompatible and nontoxic. Due to this effect used in biomolecules and ligands targeting, it has a negative charge. The optical and electrical properties optimize the shape and size of particles.

Based on these characteristics, AuNPs are used as drug carriers for treating the various disorders shown in Table **1**.

Table 1. Selection criteria of metals for colloidal drug delivery system.

Metal	Electrode Potential (V)	Electrical Resistivity (Ωcm)	Thermal Conductivity (Wm-1K -1)
Gold	+1.7	2.4	319
Platinum	+1.2	9.9	72
Copper	+0.3	1.7	403
Silver	+0.8	1.6	428
Aluminium	-1.7	2.7	238

3. GOLD NANOPARTICLES

Gold is enriched by defending the outer layer of organic ligands. It is the safest and most non-toxic because it has exceptional optical and electric properties of gold, plasmonic, and magnetic properties and an excellent surface area called metallic nanoparticles [8, 9]. Due to this, it has the best modified and possible drug loading capacity, which acts as a drug delivery carrier, as depicted in Fig. (**1**). Particle size, shape, and formulation monolayers all contribute to the multiple targeting sites made possible by the ligand place exchanging reaction, such as biomolecules [10-12], which include proteins, peptides, antibodies, *etc*.

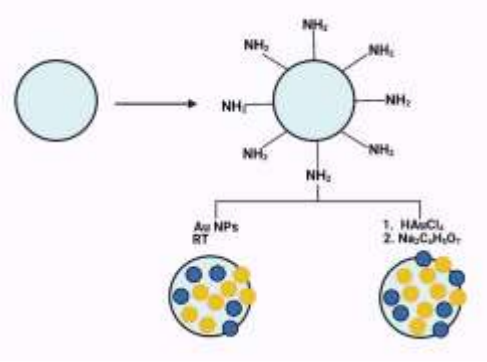

Fig. (1). Gold nanoparticles. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

The particle size range is 2-10 nm. It can be classified based on particle size range; if the particle diameter is 20-50 nm, it is the most efficient for cellular uptake Table **2**. The particle size is between 40 to 50 nm. It can quickly diffuse the tumor cells, which helps to improve it fast. However, the particle sizes, *i.e.*,75 to 100 nm, do not disperse into cancer and remain near the blood vessels. It can provide a larger surface area of 520 nm. The Thiol/gold ratio has a vital role; if the quantity of thiol (SH) is high, the particle size will be small. The gold nanoparticles are protected by the crystal structure of the thiol monolayer because it has 102 gold atoms and 44 p-MBA units. All the pharmacokinetic parameters of gold nanoparticles are presented in Table **2**.

4. TYPES OF GOLD NANOPARTICLES

Table 2. Common pharmacokinetic parameters for gold nanoparticles.*

Characters	Note
Bioavailability (F)	It is the rate and extent of the drug that reaches blood plasma and systemic circulation.
Volume of Distribution (VD)	(Vd=dose/c); it is the quantity of drug in a body (dose) to the concentration of the drug that is measured in blood, plasma, and unbound in interstitial fluid.
Clearance (Cl)	Drug clearance is determined by dividing the amount of its plasma in mg/mL by the rate at which they are removed from the body (mg/min).
Half-life (T ½)	Time in which the drug remains half of its initial amount. $T\frac{1}{2} = 0.693 \times Vd/Cl$
Mean Residence Time (MRT)	MRT is the average time for a drug entity to reside in the body.

Note: *[13, 14].

4.1. Gold Nanorods

The template approach is used to create nanorods by electrochemically depositing gold in the pores of nanoporous polycarbonate form membranes shown in Fig. (**2**), which is determined by the shaped membrane's pore diameter [15]. Various practical characteristics can influence the height of the nanorod, changing its characteristic proportion (the height divided by the width). The manufacture of Au nanorods has been described utilizing a range of methods. The pore length of the template membrane determines the diameter of the gold nanorod. On the other hand, the quantity of Au deposited within the membrane's pores can regulate the nanorod's length. Because just one monolayer of nanorods is generated, this approach has a low yield [16-18]. With the addition of AgNO3, quantifiable yields of gold nanorods can be obtained. In addition to the methods indicated above, bio-reduction [19], growth on a mica surface, and photochemical production have all been deliberate for manufacturing gold nanorods.

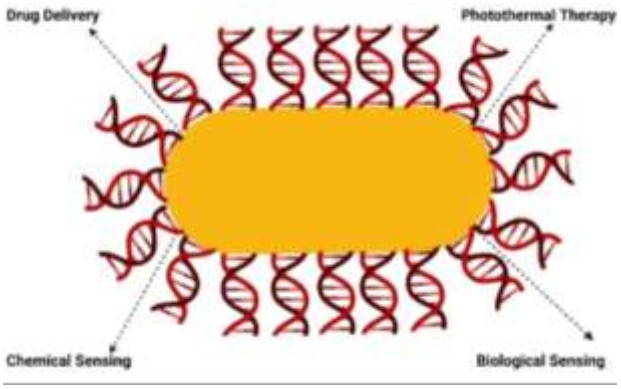

Fig. (2). Gold nanorods. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

4.2. Gold Nanoshells

A nanoshell, or nanoshell plasmon, is a sphere-shaped nanoparticle with a dielectric core and a thin Au shell covering it [20]. If it is using a quasiparticle known as a plasmon, it is a combined excitation of quantum plasma oscillation in which all of the ions' electrons oscillate simultaneously.

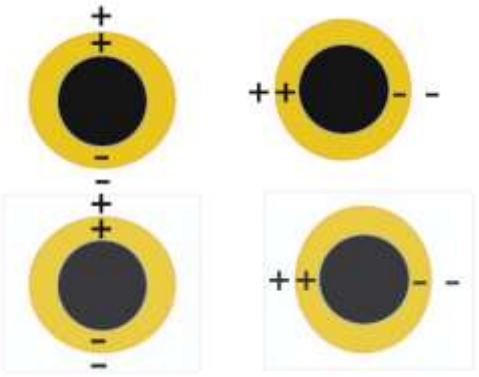

Fig. (3). Gold nanoshells. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

The tunability of the instability is connected with a mixing of the internal and external shells, which hybridize to give less or higher energy, referred to as plasmon hybridization. The lower energy forms a strong bond with the occurrence of light, whereas the superior energy forms an anti-bond and only faintly combines with it. Thinner shell layers have a more powerful hybridization contact. As a result, the wavelength of light it partners with is determined by the width of the shell and particle radius [21]. Nanoshells may be made to work in a wide range of light spectrums, including visible and near-infrared. The coupling strength is affected by the contact of light with nanoparticles, which modifies the arrangement of charges-incident light perpendicular to the substrate outcome in s-polarization (Fig. **3**). As a result, the costs are further away from the substrate surface, allowing for a more critical interface involving the shell and the core. Otherwise, a p-polarization is generated, resulting in a plasmon energy shift that is more strongly shifted, resulting in weaker contact and coupling.

In this process, the initial step in synthesizing nanoshells is creating the device where the reaction will occur. Standard photolithography was used to build microfluidic device patterns onto silicon wafers using negative photoresist SU-8 2050. The soft lithography technique was used to form the devices in poly-(dimethylsiloxane) (PDMS). It was molded onto the SU-8 masters for 4 hours at 70°C, then peeled, sliced, and cleaned. The device was pierced with a ratio of inlet and exit holes (1/16-in. o.d.). After a brief 35-second air plasma treatment, the micro-channels were irreversibly attached to a glass slip pre-coated with a thin layer of PDMS. The rectangular cross-sections of the micro-channels are 300 m wide, 155 m deep, and 0.45 m long [22].

The gold nanoparticles are prepared by Pumping “silicone oil, a mixture of gold-seeded silica and Au plating solution, and a reducing agent to the microfluidic system and nitrogen gas.

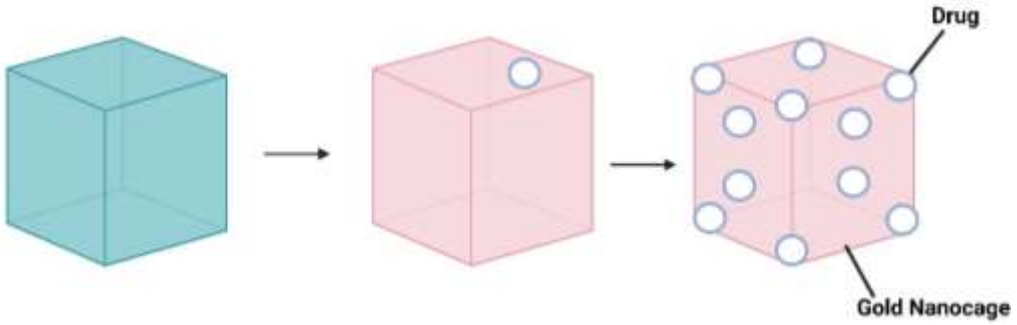

Fig. (4). Gold nanocages. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

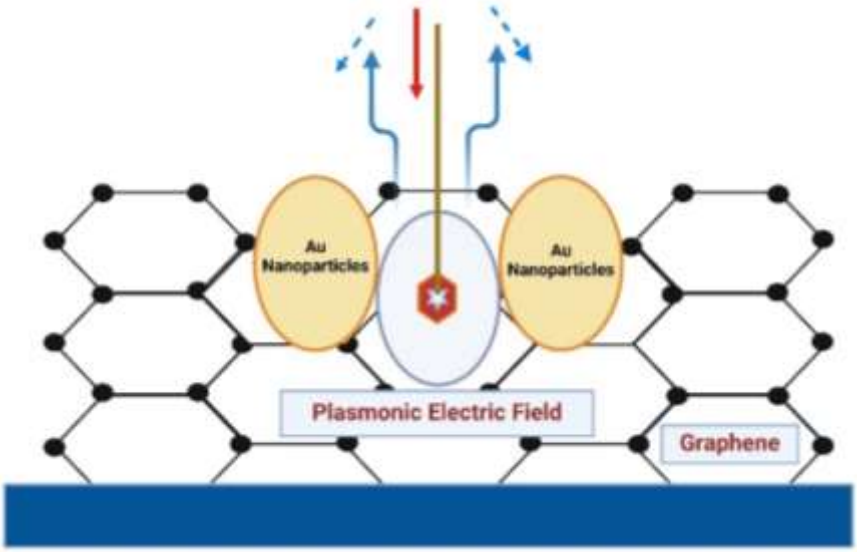

Fig. (5). SARS nanoparticles. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Then, this solution was aged for 24 hours in a controlled setting after being deposited in a centrifuge. The final liquid has an oil layer at the top and a solution underneath that contains nanoshells.

Because the Au nanoshell size and relative width can be regulated by varying in time, the reaction is allowed to run, and the concentration of the plating solution, this technology is revolutionary. As a result, researchers can modify the particles to their demands, even for cancer therapy or optics.

4.3. Gold Nanocage

In the galvanic pre-placement reaction, Au nanocage can be prepared by a reaction between truncated silver nanocubes and aqueous HAuCl, with convenient pores on the surface shown in Fig. (**4**). Polyol reduction, in which AgNO3 is reduced by ethylene glycol to produce silver atoms and then nanocrystals or seeds, can be used to create silver nanostructures with regulated morphologies. By regulating its morphology in the presence of poly(vinylpyrrolidone), a polymer able to adhere to the (100) surface selectively, the subsequent addition of silver atoms to the seeds creates the required nanostructures. Through galvanic replacement, Ag nanostructures utilized as a sacrificial template can be turned into gold nanostructures with hollow interiors [23-25]. Adjusting the ratio of silver to HAuCl4 controls the dimension and wall width of the gold nanocages.

4.4. SERS Nanoparticles

It's an optical approach that outperforms existing technologies like fluorescence and chemiluminescence in terms of sensitivity, multiplexing, strength and acts in blood and other biological matrices [26].

SERS nanoparticles (Fig. **5**) have since been used in several other studies. Gold nanospheres with a diameter of 60 nm were encoded with a Raman reporter and stabilized with a layer of thiolated polyethylene glycol (PEG) in one work [27, 28].

4.5. Gold Nanospheres

Its 2-10 nm diameter (also known as gold colloids) can be manufactured by reducing aqueous HAuCl. The citrates/gold ratio can regulate the diameter of it. It can impact the diameter of nanospheres impacted by the ratio of The thiol/gold molar due to the two-phase proportion [29]. In 1993, a two-phase process capable of creating air and heat-stable gold nanospheres of condensed dispersity and regulate dimension (10 nm) was published, enthused by Faraday's two-phase system of 1857. The low yield and the limit of utilizing water as the solvent are the method's main drawbacks. The Nanosphere will be more significant because the reduced amount of citrate is smaller (shown in Fig. **6**) [30].

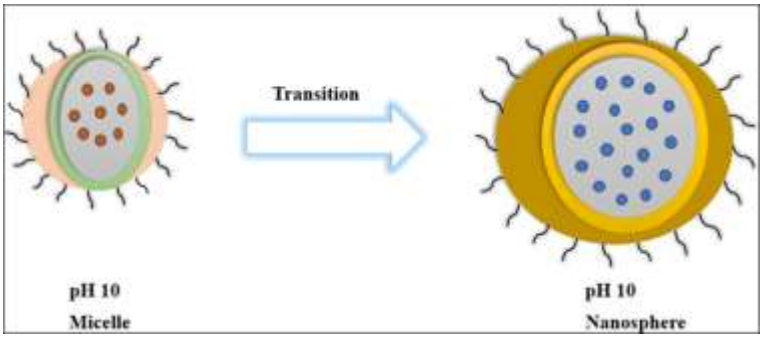

Fig. (6). Gold nanospheres. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

5. METHOD OF PREPARATIONS

There are various techniques for gold nanoparticles, such as chemical, Turkevitch/Thermal; Brust-Schiffrin; and electrochemical methods. (Shown in Fig. **7**) For the synthesis of GNPs seeding growth and other biological methods [31].

Fig. (7). Methods of preparation. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

5.1. Chemical Method

In general, there are two steps for producing AuNPs, as shown in Fig. (**8**).

(1) reduction by amino boranes, formaldehyde, citric and oxalic acids, sugars, hydrogen peroxide, carbon monoxide, sulfites, hydrogen, acetylene, and ono electronic reducing agents such as electron-rich transition-metal sandwich complexes;

(2) Stabilization by borohydrides, aminoboranes, formaldehyde, or some stabilizing agent is frequently used to prevent particle aggregation [32-34].

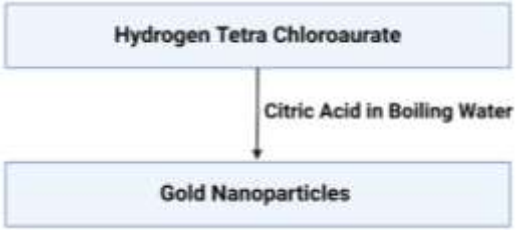

Fig. (8). Preparation of gold nanoparticles by chemical method. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

5.2. Turkevich Method

In 1951, Turkeviuch constructed this method, which reduced HAuCl4 by citrate in H_2O. This method is mostly used for the AuNPs production.

The HAuCl4 solution is cooked, and the trisodium citrate dihydrate is rapidly added to the boiling solution with continuous stirring. The color alters from bright yellow to wine in a few minutes for this method to produce 20 nm diameter AuNPs. Citrate ions serve as both stabilizing and reducing agents in this approach [35, 36].

Materials depicted in Fig. (**9**) show the creation of gold nanoparticles by a reduction in the aquatic-organic environment (Turkevich first introduced this technique in 1951).

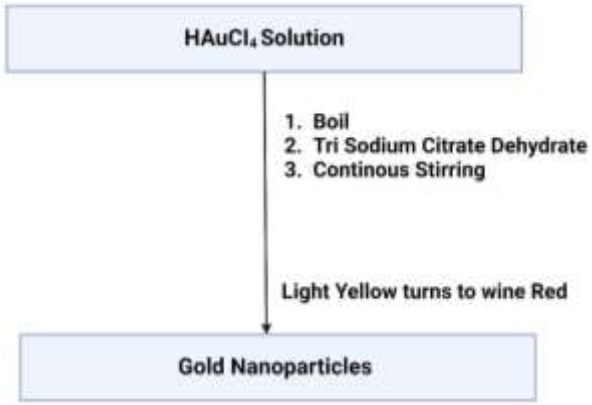

Fig. (9). Flow chart of preparation of gold nanoparticles by Turkevich Method. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

By adjusting the trisodium citrate and gold ratio, Frens improved this approach in 1973 to create gold nanoparticles of size (15 to 150 nm). Most inventors have upgradation on the Turkevich-Frens approach [37].

Kimling *et al.* observed that the small-size AuNPs stabilized by using a large amount of citrate, and a smaller amount of it caused aggregation in large particles [38]. The effect of sodium citrate on the pH of the solution and its involvement in influencing the size of the nanoparticle was recently suggested [39-41]. According to Ojea-Jiménez *et al.*, gold nanoparticles made by combining HAuCl4 with cooked sodium citrate generate nanoparticles with a narrow size range (Fig. **10**) [42].

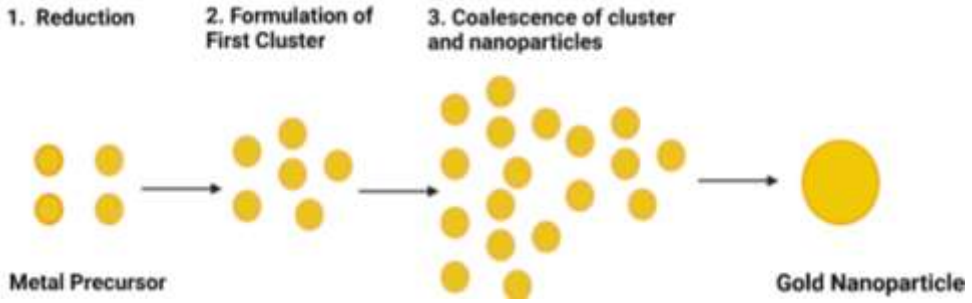

Fig. (10). Preparation of gold nanoparticles by Turkevich Method. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

5.3. The Brust-Schiffrin Method

Brust and Schiffrin developed the Brust-Schiffrin technique in 1994, as shown in Fig. (**11**). It is simple and thermostable and regulates the size and less dispersity of AuNPs. From the aqueous phase, the AuCl4 was transferred into the toluene phase with a phase-transfer agent *i.e.* tetraoctylammonium bromide. The AuCl4 also can be reduced by using NaBH4 with dodecanethiol. The reducing agent changed the organic phase's color from orange to deep brown, and AuNPs were produced [43].

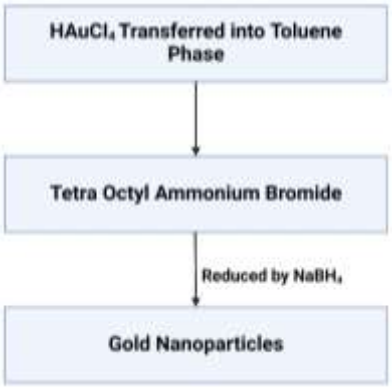

Fig. (11). Preparation of gold nanoparticles by the Brust-Schiffrin method. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

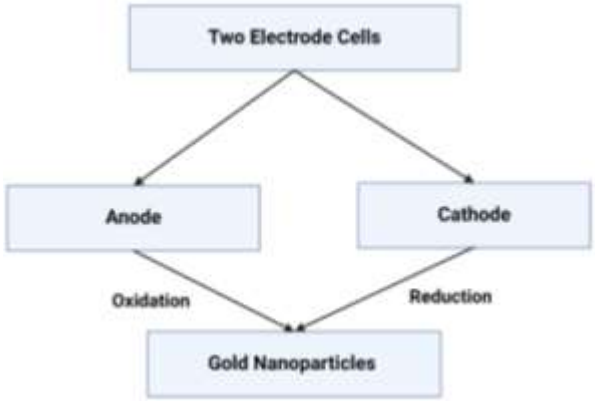

Fig. (12). Flow chart of preparation of gold nanoparticles by Electrochemical method. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

5.4. Electrochemical Method

Reetz *et al.* investigated the electrochemical production of nanoparticles in 1994 [44, 45]. The results show that employing ammonium salts of tetra alkyl as stabilizers in a non-aqueous solution produces metal particles in nanosize using the electrochemical method shown in Fig. (**12**).

5.5. Seeding Growth Method

It gives the gold nanoparticles a 540 nm diameter. By altering the metal salt and seed ratio, the particle size can also be controlled up to the 540 nm range [46]. It is simple, rapid, and economical; sodium borohydride ($NaBH^4$) was employed as a reducing agent, while trisodium citrate was used as a source of OH ions in the seeding step [47].

5.6. Biological Method

In the above method shown in Fig. (**13**), various chemicals are involved that cause harmful effects to overcome this [48]. There is a rising need for acceptable biological methods and economic nanoparticle production techniques that do not rely on toxic ingredients. Recently, Nanoparticles have been made by plant extracts and enzyme bacteria in biological processes [49].

5.7. Ionic Liquids and Gold Nanoparticles

In addition, by simply heating the quaternary ammonium ILs, stable AuNPs can be produced, as shown in Fig. (**14**). [50-53]. ILs are low-melting-point salts that are becoming increasingly relevant as solvents due to their exclusive features such as stability, non-volatile, and designable cosolvent miscibility [54]. ILs can also be used as a capping and solvent [55], templates [56], and even material precursors [57]. In a range of chemical reactions [58, 59], separations [60], and electrochemical applications [61], ILs have been widely employed.

6. APPLICATIONS

The diameter range of colloidal or metal nanoparticles is 2-20 nm, the same as biomolecules such as proteins, enzymes, or DNA. We can create novel hybrid nanoparticles by immobilizing them in various ways, such as electrostatic binding, covalent bond adsorption, and specific recognition.

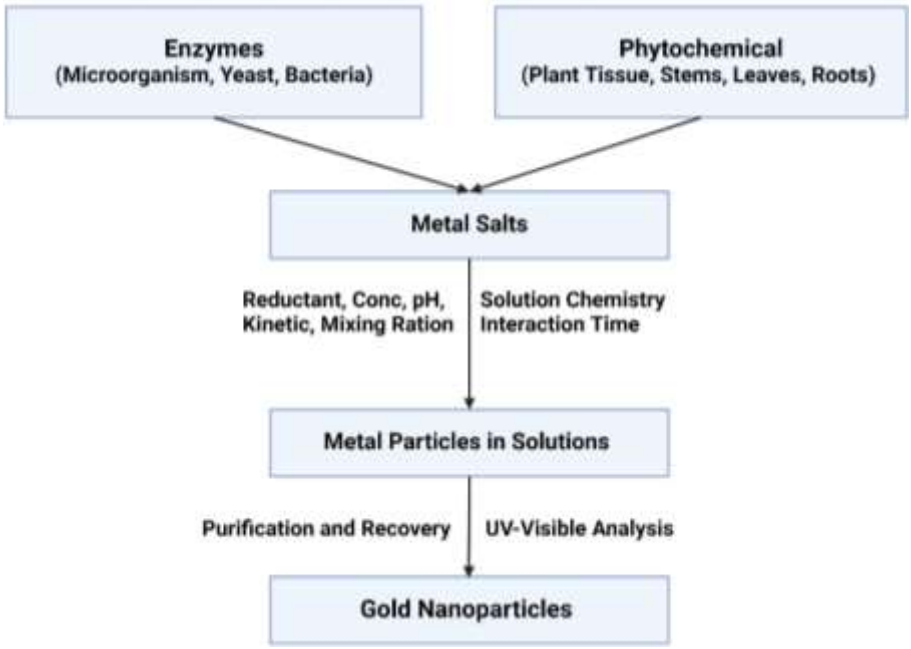

Fig. (13). Flow chart of Preparation of gold nanoparticles by Biological method. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

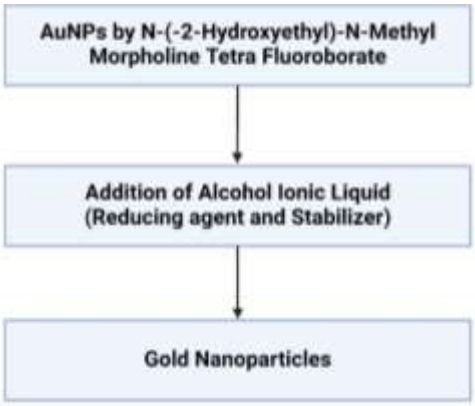

Fig. (14). Flow chart of preparation of gold nanoparticles by ionic liquids. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Various applications of gold nanoparticles are in different areas of medical sciences, as shown in Fig. (**15**).

6.1. Controlled Drug Delivery System

It is a fascinating subject of pharmaceutical sciences and development that has encouraged the researcher's interest. It may be defined as the route of releasing biologically active compounds at a special rate and place. Right now, it is critical to improve particular drug delivery modalities for their therapeutic use. Nanomaterials have a high probability of delivering numerous locus-specific drugs in treating diseases due to their tiny size, allowing them to pass through capillaries and into the cells. Particularly, AuNPs have shown significant interest in drug delivery vehicles. AuNPs may carry different therapeutics, including recombinant proteins, nucleotides, and vaccines, to their target site. These also can control drug release by internal biological stimulation.

6.2. AuNPs for Protein Delivery

The interfacial collaboration of protein and AuNPs played a significant role in the application of biologicals and biomedicines. Au nanoparticles can be employed as protein delivery carriers. Organothiol has been used as a powerful molecular probe to investigate the structure of proteins, morphology, and stability of AuNPs. The presence of organothiol in AuNPs that are coated with protein and its possible influence on the functioning and toxicity of the proteins, AuNPs should not be overlooked in biomedical and genetic sectors due to its great comparative richness in biofluids comprising serum plasma [62]. In earlier investigations, chitosan was used to functionalize AuNPs for the delivery of insulin [63]. Chitosan, a harmless biopolymer, may help to stabilize the AuNPs. Insulin adsorbs significantly on the surface of chitosan-coated particles, making them useful for transmucosal administration. It was found that AuNPs functionalize with cationic tetra-alkyl ammonium, recognize the anionic protein, and inhibit its activity *via* a complementary electrostatic interface [63]. After treating the protein-particle complex with SH, the activity of the AuNPs was improved as a result of the release of free proteins. To inject gold nanoparticles into humans, the researcher used human serum albumin or apoprotein E to conjugate with gold nanoparticles. Comparing protein-conjugated AuNPs to citrate-stabilized AuNPs showed massive liver retention reduction. We found that AuNPs are specific and efficient for diseased target organs after stable conjugation with human serum albumin and apoprotein E before intravenous administration. They have a potential role in nanomedicine and nano-pharmacology [64].

6.3. AuNPs for Vaccine Delivery

Nowadays, prophylactic vaccines are the most successful medical therapy, resulting in significant reductions in mor-

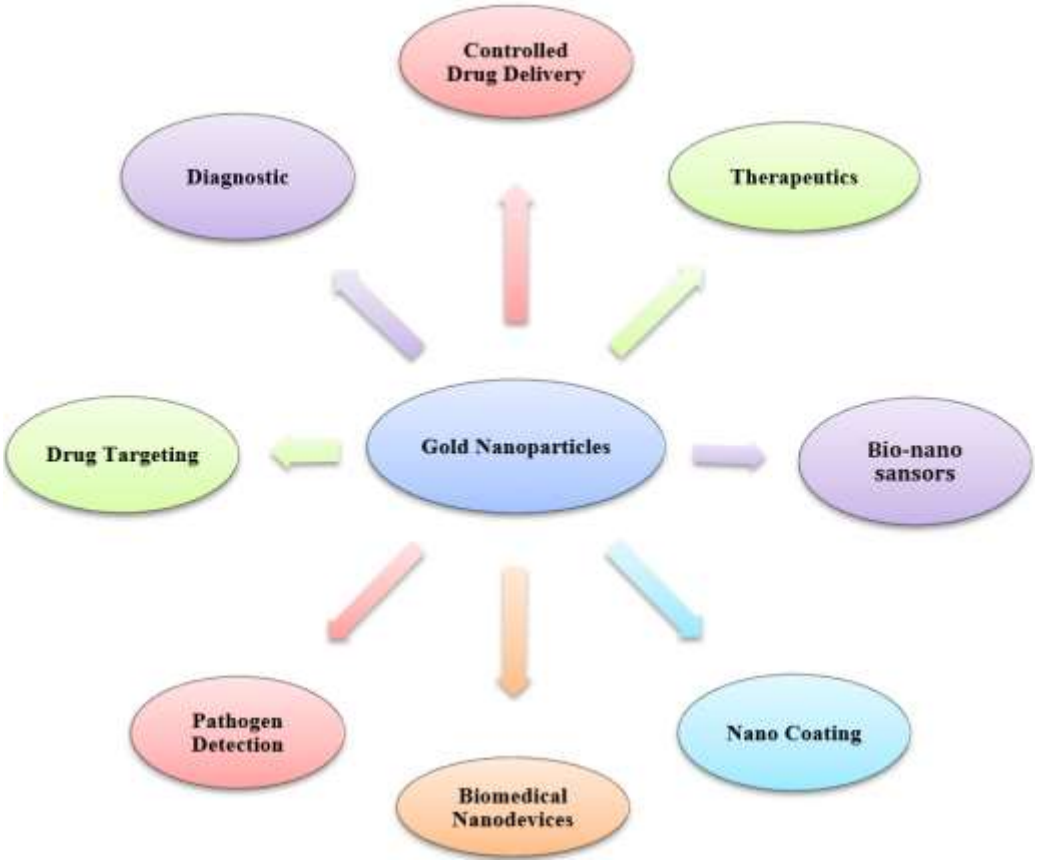

Fig. (15). Application of gold nanoparticles. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

bidity and death from various infections worldwide. The traditional way of immunizations is notably effective, but their manufacturing and distribution are limited. Therefore, AuNPs have been widely employed for vaccination purposes with potential benefits over the traditional use of vaccine delivery because of their various size and shape with customizable surface features.

Methotrexate (MTX), a folic acid analog, may disrupt folate metabolism, resulting in cytotoxic effects in cancer treatment. AuNPs containing drugs or genes may be delivered to their targets [65-68]. The conjugation of MTX to 13 nm colloidal Au yielded good outcomes [69]. Moreover, the streptomycin (an antibiotic) was directly attached to nonfunctionalized sphere-shaped Au-NPs (diameter of about 14 nm) and was able to limit the growth of bacteria effectively and constantly. AuNPs effective in developing vaccines against tick-borne encephalitis were proposed by Demenev *et al.* [70]. AuNPs became multivalent as a result of a suitable design, which improved their collaborations with target receptors. Chen and his colleagues employed three types of molecules attached to the surface of AuNRs and acted as a DNA vaccination for HIV therapy. AuNPs encapsulated with aptamer (Apt-AuNps) were produced by Shiang *et al.* as extremely potent inhibitors of HIV reverse transcriptase. Additionally, according to Liu *et al.*, AuNPs were investigated for the production of HIV/ AIDS vaccines and subjected to many great assessments to date [71-75].

6.4. Au-NPs as a Cancer Drug Delivery Agent

6.4.1. In Pancreatic Cancer

Although site-specific delivery of drugs was projected to have very few adverse effects, its few applications were due to a lack of validated technology. As a result, biomedical nanotechnology could supply the necessary estimation to further remedial science by applying novel disease treatment methods. Because of their unique physicochemical features, Au-NPs are commonly used in medication delivery. These AuNPs have been used to enhance pancreatic cancer chemotherapy [76].

Rather than using a single chemotherapeutic drug, it has recently been coupled with additional chemicals to boost its effectiveness for many solid tumors. In preclinical models, the combination of cetuximab and gemcitabine was employed. Their toxic level was relatively lower, with common side effects such as fever, skin rashes, and fatigue. The foregoing findings drew the attention of researchers and medical professionals. They prompted them to develop a nanotechnology-based alternative and better-targeted medication delivery system for tumors, particularly pancreatic cancer [77-79]. The following design was eventually used to create such a drug delivery device. In Fig. (**3**), Gemcitabine (an anti-cancer agent) was administered using the AuNPs delivery system and cetuximab C225 antibody as a targeting agent. This

system prevented the growth of pancreatic tumor cells and inhibited the formation of orthotopic pancreatic tumors as confirmed by *in vitro* and *in vivo* studies. C225 could precisely bind and activate EGFR since it was found on the cell surface. It consisted of a combination of three domains, *i.e.*, intracellular (tyrosine kinase), extracellular (ligand-binding), and hydrophobic transmembrane. As the ligand binds to the EGFR, nest phosphorylation occurs, resulting in receptor Zhomo/heterodimerization and initiation of the signaling cascade, leading to cell death [80-83]. Overexpression of a tyrosine kinase enzyme may be responsible for pancreatic cancer. Gemcitabine has the potential to inhibit the tyrosine kinase receptor and aid in the treatment of pancreatic cancer [84].

Gemcitabine could also be used as an anticancer treatment for various malignancies, such as neck, head, breast, and ovary [85-89]. As a result, the targeted drug delivery system with NPs may lower anticancer drug doses while increasing efficacy, specificity, and toxicity. Transferring various medications to metastasized locations and monitoring treatment efficacy without damaging healthy cells or tissues would be the most challenging strategy.

6.4.2. In Lung Cancer

Platinum-based anticancer agents such as Cisplatin, carboplatin, and Oxaliplatin were used widely and had the most significant role in chemotherapy. Cisplatin was officially permitted in 1971 and has been used primarily in managing testicular cancer [90]. Upon binding to DNA, Carboplatin, Cisplatin, and Oxaliplatin cause cell death by blocking their transcription and replication [90, 91]. Increased intracellular tripeptide glutathione levels, reduced cisplatin uptake, and tolerance of DNA adducts may all make cisplatin inactive. According to current research, one more probable cause of resistance is a higher concentration of intra-cellular chlorides [92].

6.5. Nano-sensing

Chemical and biological sensing is the most commonly used application of AuNPs. It offers effective sensors for the detection of a variety of analytes, including anions, metallic ions, and molecules such as nucleotides [93], proteins [94, 95], and toxins [96]. Fig. (**5**) depicts a variety of AuNP-based nano-bio sensors. The sensor has been built for the expected detection and various properties of AuNPs. Depending upon the sensing approaches, these sensors can be colorimetric, fluorescence-based, electrical and electrochemical, surface plasmon resonance, surface-enhanced Raman scattering (SERS)-based, quartz crystal microbalance-based, and Bio-Barcode assay sensors [97]. AuNPs have been used in various nano-bio sensors due to their unique properties, such as colorimetric sensing (based on visible color change owing to AuNPs aggregation). Fluorescence-based sensors exhibit quenching properties, the conductivity of electrical and electrochemical sensors, optical properties of AuNPs-based surface plasmon resonance sensors, and resonance properties of SERS-based sensors of AuNPs. The vibrational changes of Au NPs cause inelastic scattering of photons AuNPs in quartz crystal microbalance-based sensing have a large surface area, which improves detection sensitivity. The strong binding affinity of AuNPs to thiols and noticeable colour change owing to AuNPs aggregation in the AuNPs based Bio-Barcode Assay [98]. Because of their significant and distinctive optical features, gold nanorods are a popular choice for biosensing among the various forms of AuNPs. The essential markers for the creation of sensitive biosensors are optical absorbance and its variations.

6.6. Virus Detection

Various investigations use AuNP's exclusive features to construct different sophisticated viral detection systems. The design and underlying idea of the produced tests vary widely. In most of these experiments, however, AuNPs play a crucial role in conjugating unique virus-targeting biomolecules. Various bioconjugated AuNPs may be used to recognize different human viruses in other methods such as colorimetric, scanometric, electrochemical, and fluorometric methods.

6.7. HantaanVirus (HTNV)

More than 24 HTNVs that are antigenically and genetically different have recently been added to the genus Hantavirus [99]. Rodent-borne HTNVs, may cause devastating human infections such as hemorrhagic fever with renal disease and hantavirus related to COPD and hospitalize about 150,000 people every year with a 10% fatality rate. Due to an increase in the data of current research reports on newly discovered HTNVs [100-102], the health effects of HTNVs are predicted to rise drastically in the upcoming scenario. AuNPs were used to create a new immuno-PCR technique for detecting HTNV nucleocapsid protein [103]. In this method, the surface area of AuNPs was increased, which helps to produce functionalized antibody- oligonucleotide, which conjugated with explicit monoclonal antibodies for labeling the target HTNV antigen. This analysis also involves DNA barcoding for the signals' magnification. Also may be used for the detection of purity, quantification, and presence of spiked antigen samples (minimum 200 aM), which can make its magnitude seven more time-sensitive than the conventional ELISA.

This assay has a higher detection capacity and can target the HTNV nucleocapsid protein, making it a viable prospective approach for the early analysis and management of HTNV [104]. This is a large viral component that generates post-virus infection.

6.8. Coronaviridae– Severe Acute Respiratory Syndrome (SARS)

Coronavirinae and Torovirinae, two subfamilies of the Coronaviridae family, have lately been enlarged to encompass several viruses. Ther are the four genetically diverse genera of coronavirinae *i.e.*, α, β, γ and Δ coronavirus [105]. These are pleomorphic RNA viruses with a spherical or bacilliform shape (120–160 nm by 75–88 nm or 170–200 nm by 75–88 nm). They have a 27–32 kb positive-sense ssRNA genome that encodes at least 4-5 structural proteins, *i.e.*, glycoproteins (S, M), which are later processed into [106, 107]. Coronavirus can affect the respiratory system and intestine and cause hepatic and neurological diseases [108]. From the various strains, the HCoV-229E, HCoV-OC43, HCoVNL63, and HCoV-HKU1 have more extensive spreading capacity than other coronaviruses. They may cause upper respiratory

tract infections and induce mild cold-like symptoms [109-112]. Coronaviruses SARS-CoV were revealed in China in 2002, and another virus, *i.e.*, MERS-CoVwasoriginated in the Middle East in 2012; they were pathogens that can cause pneumonia or pneumonia-like situations, and the death rate at that time due to this virus was up to 35% [113, 114]. Because of its contagious nature, modern SARS detection techniques have gained a lot of interest. The goal of employing AuNPs to identify SARS is to produce a quick and specific molecular test.

Developing speedy and specific molecular detection for SARS using AuNPs mainly emphasizes two critical analyses. The first one is a technique used to detect the pp1ab gene (colorimetric technique), and the other is the nucleocapsid protein gene detection technique. The AuNPs can preferentially adsorb the ssDNA over dsDNA [115]. In this process, definite, short ssDNA probes may be attached to the outer side of AuNPs. This enhances the colloidal stability of particles, which enables them to tolerate the elevated concentration of salt, and there is no aggregation and color change. Furthermore, the adsorbed ssDNA probes generate dsDNA with the target DNA, which is then effortlessly removed, allowing the AuNPs to aggregate due to the salt.

The presence of target SARS nucleic acids is indicated by a shift in the color of the solution from red to blue, which may be seen with the naked eye or accurately measured using a UV-vis spectrometer in proportion. AuNPs enhance electrode conductivity and surface area accessible for immobilizing the detection probe in an electrochemical test [116].

The AuNP-based assays developed for the molecular detection of SARS are relatively quick and easy to use, particularly the colorimetric assay. They require no instrumentation or trained personnel and produce results exclusively in the liquid phase, which can be quickly identified as positive or negative by the naked eye within 5 minutes. Alkaline phosphate was used after labeling with streptavidin to increase the indirect decline and statement of Ag ions. The anodic stripping voltammetry quantifies these ions in fractions to the required DNA concentration. This approach can identify target SARS nucleic acids with a sensitivity limit of 100 FM, making it highly useful for early SARS virus diagnosis, which is crucial for such an infectious infection.

Furthermore, colorimetry analysis is used for more sensitive AuNP-based nucleic acid to detect another virus by little change in the methods and association with other AuNP sensing characters [117].

6.9. Hepeviridae (Hepatitis E Virus)

Hepeviridae is a family of viruses (Hepatitis E Virus). The Hepeviridae family contains only one monogeneric member, HEV, a sphere-shaped, tiny, non-enveloped single strained RNA virus (7.2 kb genome) [118]. There are three partially overlapping ORFs in a viral RNA, flanked at both ends by short untranslated regions. Four mature nonstructural proteins are encoded as the first ORF (helicase, protease, methyltransferase, and replicate), two structural proteins are encoded by the second ORF (C and VP1), and the third ORF encodes a small protein of unknown function [119, 120]. Human liver inflammation is known to be caused by HEV.

6.10. Gold Nanoparticles as Theranostic Agents

6.10.1. Diagnostic Capabilities

Explaining how gold nanoparticles can be used in various imaging techniques such as MRI, CT scans, and optical imaging due to their unique optical and electronic properties [121].

6.10.2. Therapeutic Applications

Detailing the use of gold nanoparticles in drug delivery, photothermal therapy, and radiation therapy, and how their surface can be modified to target specific disease sites.

6.10.3. Integrated Theranostic Approach

Discussing recent studies and advancements that showcase the simultaneous diagnostic and therapeutic capabilities of gold nanoparticles, providing examples of how this integration improves treatment efficacy and patient outcomes [122].

6.11. Gold Nanoparticle for Improving the Efficacy of Bioactive Compounds

6.11.1. Enhanced Stability

Discussing how coating bioactive compounds with gold nanoparticles can improve their stability and prevent degradation, thus prolonging their shelf life and therapeutic effectiveness.

6.11.2. Improved Bioavailability

Highlighting studies that demonstrate how gold nanoparticle coatings enhance the bioavailability of bioactive compounds by improving their solubility and absorption in biological systems [123].

6.11.3. Targeted Delivery

Explaining how the conjugation of bioactive compounds with gold nanoparticles allows for targeted delivery, reducing side effects and increasing the concentration of the compound at the desired site of action.

6.11.4. Synergistic Effects

Providing examples of how the combination of bioactive compounds and gold nanoparticles can result in synergistic therapeutic effects, leading to improved outcomes in various disease treatments.

6.11.5. Case Studies and Examples

Presenting specific examples and case studies where bioactive compounds' efficacy has been significantly enhanced through coating with gold nanoparticles [124].

6.12. Modern Advance Gold Nanoparticles in Clinical Trials

Various clinical trials have been done to authenticate AuNPs in cancer treatment [125, 126]. The FDA accepts

Table 3. List of clinical trials of gold nanoparticles.*

S. No.	Name	Materials	Application	Clinical Trials.gov Identifier
1	AuroLase®	Silica-gold nanoshells coated with PEG	Laser-responsive thermal ablation of solid tumors: head/neck cancer, primary and/or metastatic lung tumors.	NCT00848042, NCT01679470
2	AuroLase®	Silica-gold nanoshells coated with PEG	Prostate, head and neck, lung MRI/US fusion imaging and biopsy in combination with nanoparticle-directed focal therapy for ablation of prostate tissue.	NCT02680535
3	NU-0129	A Spherical Nucleic Acid (SNA) gold nanoparticle	Targeting BCL2L12 in recurrent glioblastoma multi-forme or gliosarcoma patients.	NCT03020017
4	Silica-gold nanoparticles	Silica-gold nanoparticles	Plasmonic photothermal therapy of flow-limiting atherosclerotic lesions.	NCT01270139
5	CNM-Au8	gold nanocrystal	Evaluation of safety, tolerability, and pharmacokinetics of CNM-Au8 in healthy male and female volunteers.	NCT02755870
6	Gold nanoparticles	Gold nanoparticles	Sensors functionalized with gold nanoparticles organic functionalized gold nanoparticles detection of gastric lesions.	NCT01420588
7	Gold nanoparticles	Gold nanoparticles	Exhaled breath olfactory signature of pulmonary arterial hypertension.	NCT02782026

Note: *[137].

some methods to diagnose the disease and its use in medicine, as confirmed by various researchers [127, 128]. These factors, such as particle size, morphology method, and environmental factors, cause the cytotoxicity of gold nanoparticles [129, 130]. Astra Zeneca collaborates with Cytimmune on a clinical trial emphasizing old nanoparticle-based cancer treatment. Their primary stage of trials goes well. A compound derived from recombinant human tumour necrosis factor-alpha (rhTNF), Aurimune (CYT-6091), was injected to disrupt the blood vessels and allow chemotherapy medicines to enter the tumour to harm the cancer cells. It was discovered that very potent dosages of rhTNF could be delivered to tumour cells safely. The researcher found the amount of rhTNF given once immobilization to it could be three times more potent without any side effects [131]. A PEG layer inhibited the uptake of nanoparticles by the mononuclear phagocytic system (MPS) and facilitated tumour mass growth through the EPR effect. The potential of AuNPs to absorb NIR light has boosted concern in PTT in recent years. Researchers are primarily interested in photothermal conversion for efficiency-specific cancer cell targeting that improves cancer cell killing along with *in vivo* nanoparticle biodistribution [132]. For example, Aurolase® (PEG-coated silica-gold nanoshells) was developed to design the thermally ablated solid tumors by Nanospectra, and a NIR light source stimulates it. This light absorption enhances the temperature for dissolving solid tumour cells [133]. There are two approaches to deliberate the safety and probability in the treatment of atherosclerosis, one using silica-gold nanoparticles and the other using silica-gold iron-bearing nanoparticles (NCT01270139) [134]. The results suggested that the first approach exhibited significant regression of atherosclerosis without any side effects.

Scientists performed clinical trials for gold nanoparticles as a novel therapeutic approach (electronic nose sensor) to evaluate the diagnosis of pulmonary arterial hypertension (NCT02782026). Additionally, randomized placebo-controlled trials were carried out on healthy humans to assess the safety and pharmacokinetics of CNM-Au8 [135]. Various clinical trials performed on gold nanoparticles are listed in Table **3** [136].

7. REGULATORY AND PATENT ASPECTS OF GOLD NANOPARTICLES

These are some regulatory and patent aspects for the gold nanoparticles [137].

7.1. Regulatory Frameworks

An overview of the current regulatory guidelines and requirements for the approval of gold nanoparticle-based products in major markets such as the United States (FDA), Europe (EMA), and other relevant regions.

7.2. Safety and Toxicity Assessments

Discussion on the necessary safety and toxicity evaluations that gold nanoparticles must undergo to meet regulatory standards, including preclinical and clinical testing protocols.

7.3. Intellectual Property and Patents

Analysis of the patent landscape for gold nanoparticles, highlighting key patents, recent trends in patent filings, and notable patent disputes or litigations.

7.4. Challenges and Opportunities

Examination of the regulatory challenges faced by developers of gold nanoparticle technologies, including issues related to standardization, quality control, and long-term stability. Additionally, exploring opportunities for innovation and collaboration within the regulatory framework.

7.5. Case Studies and Examples

Providing specific examples of gold nanoparticle-based products that have successfully navigated the regulatory and patent landscape, illustrating best practices and lessons learned [138].

8. FUTURE PROSPECTIVE OF GOLD NANOPARTICLES

The use of gold-based nanoparticles for targeted drug delivery systems holds significant promise for the future of medicine and healthcare. There is an outline of some potential future prospects and trends in this field [139].

8.1. Enhanced Targeted Therapies

Gold nanoparticles can be functionalized with various targeting ligands, such as antibodies or peptides, to specifically bind to cancer cells or diseased tissues. Future research may focus on designing even more precise and effective targeting strategies to improve the specificity and efficiency of drug delivery.

8.2. Personalized Medicine

Advances in genomics and proteomics may enable the development of personalized gold nanoparticle-based drug delivery systems. These systems could be tailored to an individual's genetic and molecular profile, optimizing treatment outcomes and reducing side effects.

8.3. Combination Therapies

Researchers are exploring the use of gold nanoparticles to deliver multiple therapeutic agents simultaneously, such as chemotherapy drugs and immunotherapies. This approach could enhance the synergistic effects of combination therapies while minimizing systemic toxicity.

8.4. Theranostics

Gold nanoparticles can serve both therapeutic and diagnostic functions in a single system, known as theranostics. Future prospects may involve the integration of imaging agents with therapeutic payloads to enable real-time monitoring of treatment responses and adjustments as needed.

8.5. Minimizing Side Effects

Continued research may focus on engineering gold nanoparticles that reduce off-target effects and toxicity, thereby improving the safety and tolerability of treatments.

8.6. Clinical Translation

As research progresses, gold nanoparticle-based drug delivery systems may move from preclinical studies to clinical trials and, eventually, commercialization. Regulatory approval and widespread clinical adoption will be key milestones in this journey.

8.7. Nanotheranostics Platforms

Integration with other nanoscale technologies, such as nanosensors and nanorobots, could lead to the development of highly sophisticated nanotheranostics platforms capable of precise drug delivery, monitoring, and therapeutic adjustments.

8.8. Multidisciplinary Collaborations

The success of gold nanoparticle-based drug delivery systems will likely depend on collaborations between researchers from various fields, including materials science, chemistry, biology, and medicine, to develop innovative solutions and address complex challenges.

8.9. Addressing Drug Resistance

Researchers may explore how gold nanoparticles can be used to overcome drug resistance mechanisms in various diseases, such as cancer, by delivering therapeutic agents in a targeted and controlled manner.

8.10. Commercialization and Accessibility

As these technologies mature, efforts to make gold nanoparticle-based delivery systems cost-effective and accessible to a broader patient population will be crucial for their widespread adoption.

It's important to note that the field of nanomedicine is rapidly evolving, and prospects will depend on ongoing research breakthroughs, technological advancements, regulatory considerations, and market dynamics. Researchers and healthcare professionals should stay informed about the latest developments in this area to harness the full potential of gold-based nanoparticles for targeted drug delivery systems [140].

CONCLUSION

Aside from drug and gene delivery, AuNPs have broad applications in photodynamic therapy (PDT), diagnosis, and imaging due to their unique properties. Gold nanoparticles of the drug are delivered to different target sites. Most of the colloidal drug and polymer combinations can be delivered to site-specific areas. Gold nanoparticles have different pharmacokinetic and pharmacodynamic characteristics, which are essential in the pharmaceutical industry. This review presents how AuNPs are synthesized and modified, their characterization techniques, and various medical applications. Several synthetic approaches to producing AuNPs have been proposed due to the low yield of a top-down approach.

The side effects of AuNPs are less because of their essential safety concern, as the researchers focused on reduced toxicity by implementing different novel and practical approaches for their preparations. Furthermore, they also have antibacterial, antifungal, anticancer, and antioxidant properties, as described in this review. In conclusion, to broaden their applications, AuNPs should be identified for their unique properties, including optical properties, drug carriers, and anticancer effects.

AUTHORS' CONTRIBUTIONS

It is hereby acknowledged that all authors have accepted responsibility for the manuscript's content and consented to its submission. They have meticulously reviewed all results and unanimously approved the final version of the manuscript.

LIST OF ABBREVIATIONS

AIDS	=	Acquired immunodeficiency syndrome
AuNPs	=	Gold Nanoparticles
Cl	=	Clearance
COPD	=	Chronic Obstructive Pulmonary Disease
CT	=	Computed Tomography
EPR	=	Enhanced permeability and retention
F	=	Bioavailability
FDA	=	Food and Drug Administration
GNPs	=	Gold Nanoparticles
HIV	=	uman immunodeficiency virus
HTNV	=	Hantaan Virus
ILs	=	Ionic Liquids
MPS	=	Mononuclear phagocytic system
MRI	=	Magnetic resonance imaging
MRT	=	Mean Residence Time
MTX	=	Methotrexate
NIR	=	Near-infrared
NLC	=	Nano lipid carriers
PDMS	=	Poly-(dimethylsiloxane)
PDT	=	Photodynamic therapy
PEG	=	Polyethylene Glycol
SARS	=	Severe Acute Respiratory Syndrome
T ½	=	Half-life
Vd	=	Volume of Distribution

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

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