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Review Article

NANOGOLD AS A COMPONENT OF ACTIVE DRUGS AND DIAGNOSTIC AGENTS

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ABSTRACT

Nanotechnology is a fast-growing field of science that dates back to the late 1950s. Nanoparticles can be divided into organic, inorganic, and carbon-based. An example of inorganic nanoparticles, in which relatively high hopes for the development of both pharmacy and medicine are placed, are gold nanoparticles. They possess beneficial properties, such as small size (ranging from several to several hundred nanometers), a large specific surface area to volume, and characteristic optical properties, as well they are relatively easy to synthesize with the ability to control the parameters of the final product to obtain desired sizes and shapes. Moreover, they exhibit high biocompatibility and low toxicity, which is especially important when administered internally (*per os, i. v.*). Several methods for the synthesis of gold nanoparticles (AuNPs) have been described in the literature, including chemical, physical, and biological methods. Microorganisms such as fungi, plants, and algae are used to produce gold nanoparticles. Due to their particle size and ability to penetrate cell membranes, gold nanoparticles are being considered as drug carriers. Many attempts have been made to attach gold nanoparticles to drugs, focusing mainly on antimicrobial and anticancer drugs. Treatment with these drugs in combination with nanoparticles is more effective than applying free drugs without the carrier. AuNPs have also been used with great success in the photothermal therapy of cancer. Additionally, work is underway to use them in diagnostics to prepare flow assays, increasing the sensitivity and specificity of the tests. Due to a large amount of scientific data on nanogold, this review focuses on presenting methods for obtaining gold nanoparticles and approximating their applications in areas of medical science.

Keywords: Nanomaterials, AuNPs, Photothermotherapy, Diagnostic, Cancer therapy

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INTRODUCTION

The precursor of nanotechnology is considered to be Richard Feynman, who, in 1959 during a lecture entitled "*There's plenty of room at the bottom*," presented the concept of engineering materials at the level of atoms [1]. One of the most interesting particles, considering their physicochemical properties, seems to be gold nanoparticles (AuNPs) [2], which have been in use since antiquity. However, it was probably Michael Faraday who first noticed the difference between the properties of colloidal and solid gold 150 y ago [3]. Nanoparticles are materials with at least one dimension in the range of 1-100 nm, and their properties depend directly on their size, shape, and particle size distribution [2]. Nanoparticles have both the properties of a solute and separate particles. Their surface-to-volume ratio is 35-45% times higher than that of macromolecules [4]. They also have other interesting physicochemical, magnetic, and optoelectric properties [2].

Nanoparticles have applications in medicine, disease diagnosis, tissue engineering, and drug carriers. Nanotechnology-based drug delivery systems are used for diseases such as cancer, diabetes, fungal and viral infections and in gene therapy [5]. Due to their unique properties, AuNPs can be used as drug carriers, providing higher bioavailability and minimizing side effects [6, 7].

Current studies [8-10] have confirmed the numerous advantages of nanogold compared to other nanomaterials, primarily due to highly optimized protocols for producing gold nanoparticles of unlimited sizes and shapes with unique properties. The possibility of modifying the surface of nanogold particles with various active ingredients expands the range of their potential biomedical applications [11]. Due to a large amount of scientific data on nanogold, this review focuses on the presentation of methods for obtaining gold nanoparticles and their application in the field of medical science.

The databases were searched from October 15, 2022, to February 27, 2023, with papers from the last 10 y considered first, followed by older publications to supplement or verify the data. Only publications in English were included. The search method for scientific articles consisted of entering keywords ranging from general ones such as gold nanoparticles, AuNPs, antibiotics, biosensors, drugs, and active substances to more specific ones such as synthesis methods, properties, diagnosis, cancer therapy, linking them together with AND and OR logical connectors.

Methods of synthesis of gold nanoparticles

Several methods of synthesizing AuNPs have been described in the literature. These include the reduction of Au^{3+} or Au^{+} ions [12], Turkevich's method [12, 13], the use of citric acid or sodium bromide as a reducing agent [14, 15] as well as the Brust-Schiffrin method [16]. Other methods, such as the reduction of chloroauric acid with ascorbic acid [17], and the seeding-growth method, which leads to the formation of gold nanotubes [14, 18], have also been mentioned. In addition, microorganisms such as fungi [19, 20], plants [21] and algae [22-25] are used to produce gold nanoparticles [3, 25].

The synthesis methods can be classified into two types based on the substrates used. The first method involves combining individual atoms or molecules to form clusters, which is commonly known as the "bottom-up" strategy. On the other hand, the second method involves breaking up concentrations of molecules or atoms to produce particles of appropriate sizes, known as the "top-down" strategy (as illustrated in fig. 1) [4].

In the "bottom-up" method, a liquid or gas precursor is typically ionized, dissociated, sublimated or evaporated, and then condensed into amorphous or crystalline nanoparticles. This method produces nanoparticles with a low number of defects and a homogeneous chemical composition containing a small number of impurities. Generally, particles smaller than 100 nm are obtained using this method. On the other hand, in the "top-down" method, a powdery starting material is broken down into smaller fragments or particles. This is achieved by applying high-energy radiation, mechanical, chemical, thermal, or electrical energy to cause abrasion, melting, evaporation, or condensation of the material. This method produces particles larger than 100 nm. The products are free of contamination from solvents and are homogeneous. However, the relatively large

amount of waste produced during synthesis makes physical processes less efficient and cost-intensive. Common physical methods for generating nanoparticles include high-energy ball milling, laser ablation, electrospraying, inert gas condensation, physical vapor deposition, laser pyrolysis, spray pyrolysis, and melt mixing [1, 4, 26].

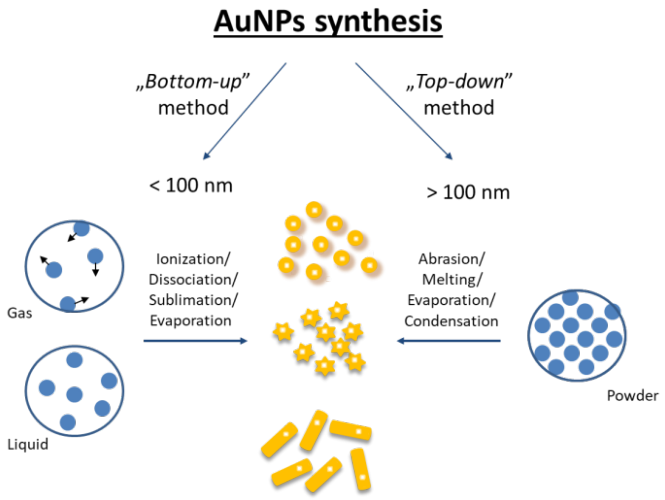

Fig. 1: Synthesis methods of gold nanoparticles according to the substrate type [1, 4, 26]

Nanoparticle synthesis methods can also be classified based on the production method: chemical, biological, and physical [2, 14]. The most common nanoparticle synthesis methods are chemical and physical techniques, including gas-phase deposition, co-precipitation, chemical reduction, hydrothermal synthesis, inert gas condensation, ion scattering, microemulsion, microwave, pulsed laser ablation, sol-gel, sonochemical, spark discharge, and matrix synthesis [4, 27].

Research has shown that several factors determine the size, shape, stability, and physicochemical properties of nanoparticles during the synthesis process. These factors include process parameters such as temperature, concentration, and more, the interaction kinetics of metal ion precursors and reducing agents and the adsorption kinetics of stabilizers and nanoparticles [2]. To control the properties and structure of nanoparticles, it is crucial to use the appropriate technique and conditions for performing the synthesis [26].

Chemical methods

Gold nanoparticles (AuNPs) can be synthesized by reducing Au^{3+} or Au^{+} ions, with the most common source of gold atoms being chloroauric acid ($HAuCl_4$). Organic compounds such as alcohols, carboxylic acids, amines, thiols, and citrate salts, as well as inorganic substances such as sodium borohydride or hydrogen peroxide, can be used as reducing agents. Additionally, a stabilizer (which may also function as a reducing agent) can be added to the solution to control growth rate, particle size, and shape and prevent aggregation. Common stabilizers include trisodium citrate dihydrate, sulfur ligands (primarily thiolates), phosphate ligands, polymers, and surfactants such as cetyltrimethylammonium bromide (CTAB). The size and shape of the nanoparticles are also influenced by substrate ratio, the presence of a stabilizer, and reaction conditions such as pH and temperature [14].

One of the most well-known methods for synthesizing nanoparticles is the Turkevich method, which was developed in 1951. This method enables the production of nanoparticles between 4 and 50 nm in size. In this method, chloroauric acid serves as the precursor, while sodium citrate is used as the reducing agent. The reaction takes place at the boiling point of the solution. By adding sodium borohydride to the reaction mixture, the process can be conducted without heating the solution, leading to the formation of nanoparticles with diameters ranging from 3.5-30 nm [14].

Another method for obtaining AuNPs is the Brust-Schiffrin method (1994). In this method, spherical nanoparticles smaller than 10 nm with high purity and thermal stability are obtained due to the strong binding of thiol ligands to the gold surface, which prevents the growth of nanoparticles above 10 nm. The process involves mixing an aqueous solution of chloroauric acid with tetraoctylammonium bromide (TOAB) in toluene, followed by the addition of 1-dodecanethiol and an aqueous solution of sodium borohydride. The resulting nanoparticles are then transferred to the organic phase. Purification involves phase separation, evaporation of the organic solvents, and washing and precipitation of the nanoparticles with ethanol, in which they are insoluble [14].

Synthesis by the seeding-growth method is a multi-step process that leads to the formation of different shapes of gold nanoparticles like nanowires, rods, ovals, and spheres. Initially, the precursor is reduced (as in the Turkevich method or Brust-Schiffrin) [28]. In the next step, the gold atoms assemble on the gold seeds' surface. The aggregation and nucleation are prevented by adding for example, cationic surfactants such as cetyltrimethylammonium bromide (CTAB) and a quaternary ammonium surfactant and a small amount of other ions, which induces the growth of gold into nanowires [14, 28].

There are also many other methods for nanoparticle synthesis sol-gel method, microemulsion, hydrothermal synthesis, polyol method, chemical vapor synthesis, and plasma-enhanced chemical vapor deposition [1].

Biological methods-bionanotechnology

The development of reliable, non-toxic, and environmentally friendly methods for nanoparticle synthesis has significant implications for biomedical applications. Enzymatic processes can eliminate the use of expensive chemical reagents, and they are also considered more environmentally friendly and less energy-intensive than chemical methods [3]. Interestingly, biologically synthesized nanoparticles tend to exhibit higher antimicrobial activity than conventionally synthesized nanoparticles. This is thought to be due to the synergistic proteins involved in the blocking and stabilization of nanoparticles [2].

AuNPs can be produced intracellularly or extracellularly by bacteria such as *Rhodococcus sp.*, *Thermomonospora sp.*, and *Pseudomonas sp*. In the intracellular method, Au^{3+} ions diffuse from the precursor through the cell membrane into the cell, where enzymes and other molecules are present in the cytoplasm reducing the gold ions to free Au° atoms, resulting in the formation of nanoparticles. In the extracellular method, on the other hand, the reduction takes place at the cell membrane, where Au^{3+} ions are retained by membrane enzymes that catalyze the reduction of gold atoms or in the

extracellular space with NADPH-dependent enzymes that are secreted by the bacterial cell into the extracellular space. With the intracellular method, the isolation of the final products is easier. By manipulating the growth conditions of the microorganisms, it is possible to control the shape and size of the nanoparticles obtained. Typically, particles sized up to 30 nm with a spherical shape are obtained with this method. The synthesis of AuNPs using microorganisms is a challenging process and requires additional precautions related to potential microbial contamination, making it time-consuming. These disadvantages limit the use of bacteria for the synthesis of AuNPs, although it is an intriguing area of research [2, 3, 25].

Table 1: Examples of AuNPs nanoparticles synthesis methods

Method type	Example	Nanoparticle size	References
Chemical	*Turkevich* method: $HAuCl_4$+$C_3H_4(OH)(COONa)_3$	4.0-50 nm	
	Turkevich method: $HAuCl_4$+$C_3H_4(OH)(COONa)_3$+$NaBH_4$	3.5-30 nm	[14, 28]
	Brust-Schiffrin method: $HClO_2$+TOAB+1-dodecanethiol+$NaBH_4$	<10 nm	[14, 28]
Biological	Bacteria e. g. *Rhodococcus sp*., *Thermomonospora sp*., *Pseudomonas sp*.	<30 nm	[2, 3, 25]
	Fungi e. g. *Fusarium oxysporum, Verticillium sp*.	20-40 nm	[2, 25]
	Algee e. g. *Gracilaria corticana, Acanthophora spicifera, Prasiola crispa, Chlorella pyrenoidusa and Sargassum wightii*		[2, 25]
	Plants e. g. *Salix alba*, *Garcinia mangostana*, *Terminalia arjuna*, *Guazuma ulmifolia*		[25]
Physical	Sputter deposition	-	[29-31]
	Electrospraying		[32]
	Inert Gas Condensation	5 nm	[33]
	E-beam evaporation on multi-wall carbon nanotubes by	<30 nm	[34]

Fungi can produce enzymes that have applications in the production of various metabolites via the extracellular pathway. The enzymes capable of reducing gold Au^{3+} ions derived from fungal cells include hemicellulase, acetyl oxylammonium esterase, and 3-glucanase. The AuNPs obtained by this method are approximately 20-40 nm in diameter and spherical. Fungi such as *Fusarium oxysporum* are used for the extracellular production of gold-silver nanoparticles, and fungi of the *Verticillium sp*. family are used for the intracellular production of gold nanoparticles [2, 25].

Attempts have also been made to synthesize gold nanoparticles using algae such as *Gracilaria corticana, Acanthophora spicifera, Prasiola crispa, Chlorella pyrenoidusa*, and *Sargassum wightii*. The hydroxyl and carbonyl functional groups present in their biomass are responsible for the reduction of gold ions [2, 25].

A promising direction for the biosynthesis of gold nanoparticles is the utilization of plants. Various plant parts and extracts can be used for the synthesis of AuNPs. Plants contain compounds such as flavonoids, phytosterols, alkaloids, and quinones, which are present in various organs and can act as a reductant or stabilizer in the obtaining process of AuNPs. The great advantage of the synthesis using plants is the short duration of the process, which can take only a few minutes. This is due to the higher concentration of compounds with reducing potential present in plant tissues compared to bacterial or fungal cells. In addition, the reaction is relatively easy to carry out as all substrates are combined in one vessel, and by changing various parameters such as temperature, pressure, and substrate concentrations, the shape and size of the nanoparticles obtained can be controlled. Plants such as *Salix alba, Garcinia mangostana, Terminalia arjuna, Guazuma ulmifolia*, and many others have been used to produce gold nanoparticles. This is an environmentally friendly method that allows the use of waste such as fruit peels or leaves and is not time-consuming [25].

Physical methods

In physical methods, different energy sources can be used to produce nanoparticles, including mechanical pressure, radiation, and thermal or electrical energy for material abrasion, melting, evaporation, or condensation. The advantages of these methods include the absence of solvent contamination of the final product and the production of homogeneous, monodisperse particles. However, abundant waste is produced. The most common methods used to produce AuNPs are high-energy ball milling, laser ablation, electrospraying, inert gas condensation, physical vapor deposition, laser pyrolysis, flash spray pyrolysis, and melt mixing [1].

The properties of gold nanoparticles

AuNPs can take various shapes and forms, such as spherical rods, tubes, and triangles [28]. AuNPs absorb radiation with wavelengths in the green colour range, which is why the characteristic red colour of the solution (complementary colour) is observed. However, depending on the level of aggregation of the particles, the colour can change from red to blue. This is mainly influenced by the excess of precursor used during the synthesis [14]. The diameter of the nanoparticles can be determined from the UV-VIS spectra due to the correlation between nanoparticle size and the wavelength of the absorbance peak [35].

The biomedical applications of gold nanoparticles (AuNPs) are due to their ease of synthesis, stabilisation and functionalisation, relatively low toxicity and ease of detection [25]. The high specific surface area-to-volume ratio of AuNPs influences their biological activity profile. Moreover, the shape and size of the obtained AuNPs play a crucial role in their biocompatibility, which is of great importance for their application in medical therapies [28].

The properties of AuNPs are caused by the high percentage of surface atoms and their delocalised electrons, which behave like plasmonic waves. The relatively large surface area for ligand binding allows modification and functionalisation of the particles [36]. AuNPs can be conjugated with several groups, including therapeutic agents, DNA, amino acids, proteins, peptides, and oligonucleotides. AuNPs have been shown not only to infiltrate blood vessels to reach the tumour but also to penetrate cell organelles, suggesting that they can be used as effective drug carriers. Furthermore, once the gold nanoparticles reach their target site, they can release their cargo under the influence of an external or internal stimulus [25].

The main obstacles associated with the commercialisation of nanoparticles are the challenges in scaling up their production, low efficiency of drug incorporation, and toxicity [28].

The toxicity of particles is believed to be influenced by the extent of their uptake into cells. When tested on PC3 cells, triangular gold nanoparticles were found to be absorbed in small amounts but exhibit high toxicity. Similarly, spherical gold nanoparticles showed a comparable level of toxicity but with the highest degree of cellular uptake among all the shapes tested. In contrast, nanoparticles shaped like tubes and cubes demonstrated much lower toxicity, indicating higher biocompatibility [37].

Gold nanoparticles can induce cellular oxidative stress and increase the production of reactive oxygen species when absorbed into cells, leading to DNA damage and potentially triggering apoptosis or necrosis [38].

The toxicity of AuNPs can also depend on the stabilizer used during their synthesis. Studies have found that nanoparticles stabilized with amino acids tend to be taken up by cells more readily than those stabilized with citric acid or CTAB. Certain amino acids, such as tyrosine and tryptophan, which contain an aromatic ring in their structural formula, are particularly effective in promoting the penetration of AuNPs into cells [37].

Application of gold nanoparticles in the field of medical science

The development and increased availability of modern technologies have sparked a growing interest in micro-and nanomaterials for medical and pharmaceutical applications. Their therapeutic potential has been recognized in numerous works throughout history, including those by Paracelsus, Descartes, Antoine Lecoq, and Frederic Hoffman. These authors described the effectiveness of using gold in the treatment of various conditions such as rheumatic, venereal, and skin diseases, as well as depression, migraine, epilepsy, fever, impotence, and alcoholism [39].

In recent years, gold nanoparticles have been increasingly used as drug carriers in medicine. Due to their small size (a few tens of nanometers), they can penetrate cell membranes more efficiently than other carriers, delivering chemical compounds to specific tissues and organs. Gold nanoparticles have great potential for enhancing the effectiveness of active drugs, especially those with antimicrobial potential. They can be absorbed by inhalation and ingestion and can penetrate deep into the epidermis and dermis. However, there is limited evidence of their absorption through the skin. Gold nanoparticles tend to accumulate primarily in the liver and spleen, but can also reach other internal organs such as the lungs, kidneys, heart, and brain. They can cross the blood-brain barrier, which makes them a promising tool for drug delivery to the central nervous system [40].

Gold nanoparticles coated with various drugs and active substances can facilitate their penetration into cells, making them a promising tool for detecting and eradicating cancer cells. Studies have shown that the adherence of drugs such as methotrexate and doxorubicin to AuNPs with diameters of 13 and 30 nm leads to more effective therapy compared to the use of free drugs, due to the possibility of accumulation of conjugates in tumour cells [41].

Similar conclusions were drawn from a study in which AuNPs were combined with bleomycin and doxorubicin. The resulting conjugates were characterized by high stability and specificity of action on tumour cells, allowing for the achievement of the same cytotoxic activity with lower doses compared to the traditional form of bleomycin and doxorubicin administration [42, 43].

Equally satisfactory results, confirming the benefits of nanoparticles in anticancer therapy, were obtained by combining AuNPs with folic acid and chlorambucil. The conjugates demonstrated higher cytotoxicity against cancer cells compared to free chlorambucil [44]. Numerous drugs, such as doxorubicin, cisplatin, paclitaxel, gemcitabine, methotrexate, and 5-fluorouracil can be attached to gold nanoparticles. In each of these cases, gold nanoparticles can improve the effectiveness of treatment and reduce the toxicity of drugs to body tissues [45].

Gold has demonstrated antimicrobial properties, and research has been conducted to use nanoparticles as carriers for antibiotics. Burygin and colleagues attempted to attach gentamicin to gold nanoparticles [46]. Bhattacharya's research also targeted gold nanoparticles, where aminoglycosides such as ampicillin, streptomycin, and kanamycin were attached to them [47]. The formed conjugates are characterized by increased potency and reduced toxicity compared to traditional antibiotic administration. Antibiotic-coated gold nanoparticles can penetrate bacterial cells more easily and quickly than unbound drug molecules, which has a beneficial effect on reducing the time of infection. Additionally, these combinations can demonstrate a protective effect against the action of β-lactamase enzymes, among others [48]. Several studies have demonstrated the effectiveness of antibiotic-nanoparticle conjugates, with vancomycin attachment to AuNPs reducing the MIC by 16-32 times and 8 times for VRE (vancomycin-resistant *Enterococcus*) and VRSA (vancomycin-resistant *Streptococcus aureus*) strains, respectively, compared to the effects obtained after the administration of free vancomycin [45].

Based on *ex vivo* studies, it has been shown that AuNPs can penetrate deep into the epidermis and dermis. In studies on the penetration of different types of AuNPs based on human and mouse models of skin, it was proven that spherical nanoparticles could penetrate up to 10 times more easily into the skin, especially into the *stratum corneum*. It is worth noting that increasing the hydrophobic properties of the resulting conjugates can improve their ability to penetrate the *stratum corneum* [49].

The use of nanoparticle conjugates with gentamicin in animal models of streptococcal infection showed higher accumulation of the drug at the site of infection compared to the application of non-carrier-bound antibiotics. Similarly, studies with fluorouracil nanoparticle conjugates showed twice the absorption of the drug substance from the cream compared to the penetration of non-carrier-bound fluorouracil [50]. The application of a fluorouracil-loaded AuNPs cream and gel resulted in an 18-and a 7-fold reduction in tumor volume, respectively, compared to the control group, confirming the beneficial effect of the nanoparticle conjugates in the topical administration of the drug on the skin [51].

Gold nanoparticles can be used with active drugs such as anti-inflammatory drugs, antifungal, antibacterial and antivirus drugs. These data are presented in Table 2. Nanogold can be also used for spectral detection of antibiotics for example, penicillin [52] and tetracycline [53] in food such as milk.

Table 2: Examples of nanogold particles combined with pharmaceuticals

Active pharmaceutical ingredient	The effect of the addition of gold nanoparticles	References
Ampicillin	A promising antimicrobial activity against ampicillin-resistant *Escherichia coli*	[54]
Ciprofloxacin	A promising tool for *Enterococcus* faecalis-induced infections	[55]
Vancomycin	More effective against vancomycin-resistant *S. aureus*	[56]
Aminoglycosidic antibiotics	More effective inhibitions zone for *E. coli*, *P. aeruginosa, S. aureus, and Micrococcus luteus*	[57]
5-Fluorouracil	More effective inhibitions zone for *E. coli, P. aeruginosa, S. aureus, and Micrococcus luteus*	[58]
Kanamycin	More effective against *E. coli DH5a, M. luteus, and S. aureus*	[59]
Curcumin	AuNPs increase the cytotoxicity and apoptotic effect of curcumin on cancer cells	[60]
Resveratrol	Potential better anti-cancer effect than Resveratrol alone *in vitro* and *in vivo*	[61]

Photothermal treatment of cancers

Photothermal therapy is based on the use of compounds capable of inducing local heating of tissue due to the absorption of laser light. The essence of the therapy is the administration of substances capable of penetrating the tumor cells. These cells are then irradiated with a laser, which causes electron excitation. The substances delivered in this way give off energy in the form of heat. This causes the temperature of the tissue to rise locally, resulting in damage to the cells within. Natural chromophores such as melanin are photothermal factors. However, they are characterized by low light absorption capacity and relatively inefficient conversion of the absorbed energy into heat. To damage cancer cells, a temperature of about 43 °C must be achieved and maintained for at least 15 min. One limitation of the method is the penetration of the laser into the skin, which is only about 10 cm, resulting in effective therapy of tumors located up to 2-3 cm below the skin surface [62].

Due to their high biocompatibility, ability to easily obtain desired shapes, and ability to bind drugs, AuNPs are good candidates as photothermal agents for cancer treatment. It is possible to tailor the optical properties of the nanoparticles to maximize the effects of photothermal therapy, as they can be easily modified to obtain virtually any shape. Additionally, nanoparticles' ability to attach to

drugs allows for the development of a form that can perform simultaneous photothermal treatment and chemotherapy, immunotherapy, or gene regulation [63].

AuNPs have a very high ability to absorb laser light compared to conventional photothermal compounds. Their absorption cross-section is about 4 times larger, which is associated with a much higher ability to transfer heat to the environment. This makes photothermal therapy more effective with AuNPs. Furthermore, because of the high absorption capacity, lower laser energy can be used, resulting in less invasive treatment of the body [39].

AuNPs emit heat upon irradiation with light in the range of 700-800 nm. However, for their local heating to contribute to the effectiveness of therapy, the nanoparticles must penetrate the tumor-affected tissue. To increase the permeability of blood vessels within tumour lesions and improve penetration into tumour tissues, AuNPs are coated with biocompatible poly (ethylene glycol) (PEG). The conjugates formed selectively accumulate within tumour lesions. To further increase their selectivity, targeted therapy based on the antigen-antibody mechanism can be used. This involves attaching relevant antibodies to nanoparticles that demonstrate the ability to recognize cancer cells. For example, for cervical cancer cells, anti-EGFR antibodies have found application [6, 39].

Application of gold nanoparticles in diagnostics

The flow tests

AuNPs can indeed take on a variety of shapes, sizes, and structures and their surface can be modified to be hydrophilic or hydrophobic and have a positive or negative charge. However, it should be noted that the ability to modify the surface of AuNPs is not limited to just these properties. Other modifications, such as the attachment of targeting ligands or drug molecules, can also be made to the surface of AuNPs to enhance their specificity and therapeutic efficacy [39].

AuNPs can be used for pathogen detection by exploiting their ability to interact with biological molecules. For example, they have been used in colorimetric sensors for detecting viruses, bacteria, and other pathogens in food to determine shelf-life. AuNPs can also be used in laboratory diagnostics as a biomarker for various diseases, including heart disease, cancer, and infections. They are also commonly used in immunoassays, such as pregnancy and drug tests, due to their ability to specifically bind proteins.

The use of AuNPs in the production of diagnostic tests can significantly enhance analytical performance. The incorporation of gold nanoparticles into the test membrane, for example in lateral flow assays, can increase the measurement accuracy and sensitivity of the test. AuNPs can also be used as labels for detection in immunoassays, such as ELISA, resulting in greater sensitivity and shorter assay times [64]. To be more accurate, the use of AuNPs in flow assays has enabled the determination of ferritin, which serves as a biomarker for various diseases, including lung cancer. Also, HIV strip tests containing AuNPs have shown improved analytical performance compared to conventional ELISA-based methods due to their greater sensitivity and specificity, as well as the shorter time (up to several minutes) required to obtain a result [65]. Moreover, nanoparticles with iron oxide as the core and gold as the outer layer, coated with polyacrylamide, are used to prepare sensitive and inexpensive tests to aid in the diagnosis of syphilis caused by the bacterium *Treponema pallidum* [65].

Diagnostic microfluidics

The main idea behind microfluidics is to use minimal sample and reagent volumes to perform fast, inexpensive and high-sensitivity analyses based on laboratory chips. This involves chips no larger than a microscope slide that include a system of channels and chambers to carry out chemical reactions. The chips are connected by channels to a system of pumps, valves and sensors that ensure a constant flow of fluids and the delivery of essential nutrients and oxygen to the cells. The whole process takes place on a microscale, which allows for precise control of the reaction conditions and provides greater analytical efficiency compared to conventional methods [66].

Nanoparticles with iron oxide as the core, chitosan as the intermediate layer and gold as the outer layer with attached antibodies have been used to create a test that evaluates glycated haemoglobin (HbA1c) in the blood. Such nanoparticles coat a chip into which a small amount of blood is inserted. The chip is connected to an analyzer, which gives an accurate determination in less than 30 min [64].

A similar system was used to diagnose prostate cancer by creating a biosensor to determine PSA and IL-6 levels. The electrode surface was coated with glutathione-modified AuNPs with attached antibodies. The use of nanoparticles allowed for an increase in antibody binding surface area and analytical sensitivity, making it possible to detect less than 1 pg/ml of tumor markers [64]. Other diagnostic and medical applications are presented in table 3.

Table 3: Examples of diagnostic and medical applications of AuNPs

Application	Brief description	References
Computed tomography (CT) imaging	AuNPs can be used as contrast in CT imaging. This allows for more detailed images of anatomy and pathology, which can lead to better diagnosis and treatment.	[67]
Neurodegenerative diseases	Neuroprotective role in AD, Nanogold induces anti-inflammation against oxidative stress-induced.	[68, 69]
Particle labeling and letection using Raman Spectroscopy	Gold nanoparticles can be used as probes in Raman spectroscopy. Combining this technology with gold nanoparticles could increase the sensitivity and resolution of the technique, which could help detect very low levels of chemical compounds.	[70, 71]
Cancer detection using gold nanoparticles	Gold nanoparticles can be used to detect and monitor cancer by linking them to cancer biomarkers. This allows for an early and accurate diagnosis, which can lead to better treatment and improved outcomes for the patient.	[72]
SARS-CoV-2 detection	Oligonucleotides conjugated to gold nanoparticles (AuNPs) can be used to detect Cas13a.	[73]
Detection of glucose in diabetic tears	The non-invasive detection of glucose in tears using The GMXeP (gold nanoparticles with MXene nanosheets loaded on paper.	[74]
Detection and identification of infectious diseases and biothreats	Gold nanoparticles are used as diagnostic probes in the detection of infectious diseases such as viral hepatitis, HIV and pneumonia.	[75]
Cardiac failure detection	Gold nanoparticles are used as a diagnostic tool in the functioning of the circulatory system and the diagnosis of heart diseases. It can be used to detect highly expressed genes: follistatin-related protein 1 (FSTL1) in heart failure.	[76]

Limitations and future perspective of gold nanoparticles

There are some limitations to using gold nanoparticles that need to be considered before the commercialization process of the final product. The most important ones include toxicity, stability, and cost [77, 78]. Some authors also discuss size and biodegradability as limitations [79]. The toxicity of AuNPs is especially important to assess at high concentrations before application in the field of medicine and pharmacy. Agglomeration can reduce their biological properties and activity [80]. Gold is relatively expensive to produce,

which can be a limiting factor for commercialization. The size of nanoparticles affects their physicochemical properties and, consequently, their application. Too small particles may be eliminated from the body quickly, while too large ones may have limited tissue penetration ability. Gold nanoparticles are not biodegradable and may remain in the body long-term, so it's important to conduct studies on their impact on the body, especially in the longer term [81].

In the field of medicine, using gold nanoparticles can be perspective and promising. The most important field of using gold nanoparticles is the treatment of cancer because nanoparticles can accumulate in cancer cells and show anticancer effects [82]. Applications in neurodegenerative diseases also appear promising due to their ability to penetrate the blood-brain barrier [83]. Diagnostics and pathological state detection are further application possibilities that will certainly be developed. Drug carriers are another field of using of AuNPs [84], for which numerous studies are ongoing. Due to their small size and ability to penetrate biological barriers, gold nanoparticles can help deliver drugs to the therapeutic target. AuNPs can also be used as compounds with antimicrobial activity [85]. However, further research and clinical trials are needed to confirm the efficacy and safety of these applications. It is important to consider the limitations of using gold nanoparticles, including their toxicity, stability, cost, size, and non-biodegradability. Therefore, it is necessary to conduct studies on their long-term impact on the body to ensure their safe use in medical applications.

CONCLUSION

AuNPs appear to be a promising component of drug formulation with relatively high application potential. On the one hand, they may improve the effectiveness of therapies while reducing side effects. On the other hand, they can enhance the effectiveness of antibiotics or anti-cancer drugs. Additional applications for diagnostic purposes or photothermal therapy further support the use of AuNPs. Moreover, the ease of synthesis and ability to tune their physicochemical properties supports the use of AuNPs in the treatment of certain diseases. However, it is important to assess the safety of using this form of the drug carefully, as more studies are needed to fully understand its potential toxicity. For now, AuNPs seem to have more advantages than disadvantages, and ongoing research and clinical trials will help to determine their efficacy and safety for different applications.

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All the authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

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