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Advance in gold nanoparticle- mediated drug delivery system

Shriyog V Amalkar, Pooja R Hatwar *, Ravindra L Bakal and Nitin B Kohale

Department of Pharmaceutics, Shri Swami Samarth Institute of Pharmacy, At Parsodi, Dhamangoan Rly, Dist -Amravati (444709) Maharashtra, India.

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Abstract

Gold nanoparticles (AuNPs) have emerged as versatile platforms for biomedical applications, particularly in cancer research, diagnostics, and therapy. AuNPs exhibit unique optical, electrical, and photothermal properties, making them ideal for sensing, imaging, and targeted therapy. Recent advancements in AuNP synthesis methods, characterization techniques, and applications are highlighted. Various methods, including chemical reduction, green synthesis, and hydrothermal synthesis, can produce AuNPs with controlled sizes and shapes. AuNPs have shown potential in cancer treatment, including ferroptosis induction, drug delivery, and imaging. However, limitations remain concerns. Future directions focus on enhancing stability, biocompatibility, targeting, and drug delivery capacity. AuNP-mediated drug delivery systems offer advantages over traditional medications and other nanocarriers.

Keywords: Gold Nanoparticles; Synthesis; Biomedical applications; Ferroptosis; Lipid Metabolism

1. Introduction

According to an EU statement from 2011, 2011/696/EU, materials composed of unbound or aggregated particles with one or more exterior diameters falling between 1 and 100 nm are referred to as nanomaterials. As a member of the nanomaterials group, nanoparticles are described as entities having three exterior nanoscale dimensions (1). By using extremely specific and sensitive diagnostic methods, it is possible to detect viral infections quickly, direct and start appropriate controls, and ultimately stop their spread (2). Most AuNPs (gold nanoparticles) never reach their intended target organs. Instead, they are taken up by members of the mononuclear phagocyte system (MPS), such as macrophages, primarily accumulating in organs like the liver and spleen, which have fenestrated vasculature (3). Among the most researched nanostructures for biomedical applications in cancer therapy and detection are carbon nanotubes, polymeric nanoparticles, metallic nanoparticles, microbially produced nanoparticles, liposomes, and magnetic nanoparticles (4). The shapes of nanoparticles (NPs) rod, triangular, polyhedral, octagonal, and round are used to characterize them of these, metal NPs have drawn increasing attention recently because of a unique feature (5). Compared to other nanostructures, their application is more archaic, and gold particles were utilized in China and India to prepare ayurvedic medicine (6). Unfortunately, because these treatments destroy the surrounding healthy tissues, they frequently induce several side effects. Lower survival rates are also a consequence of delayed diagnosis and a high relapse rate. By enabling simultaneous detection and treatment, treating cancer cells using a drug delivery technique based on nanoparticles is a crucial step towards addressing the drawbacks of traditional treatment approaches (7). Various Cancer stem cells (CSC) markers have been found and are being considered, despite the existing lack of knowledge regarding CSC lung biology (8). Applications for metallic nanoparticles in chemistry, physics, and biology are possible because their unparalleled photothermal, electrical, and optical qualities (9,10)

* Corresponding author: Pooja R Hatwar https://orcid.org/0000-0002-5424-3425

1.1. Metal Nanoparticles in medicine

It has been possible to successfully synthesize metallic nanoparticles and use them as components of nanomaterials or in combination with biomolecules. Generating stable, enzyme-resistant conjugates with biological elements, such as ligands, drugs, antibodies, peptides, nucleic acids, etc., is essential for therapeutic and diagnostic purposes. However, it is crucial to use building blocks that are biocompatible and able to be synthesized in relatively large quantities (at least gram scale) to successfully introduce such devices into biological systems. These methods have made use of metal nanoparticles, the most extensively researched of which are gold, silver, or platinum nanoparticles. (1)

1.2. Gold nanoparticles

Gold nanoparticles (AuNP) are the most widely used and have been the standard option for numerous studies for a number of reasons. The most significant ones are their physicochemical properties, low cytotoxicity, enzymatic stability, and chemical resistivity (for additional details on gold nanoparticles and their properties (1). Because reagents are readily available, the chemical procedure is the most well-known and frequently used technique, with the selected reducing agent impacting the particle size of the generated colloids, which can vary from 1 to 100 nm. (11).

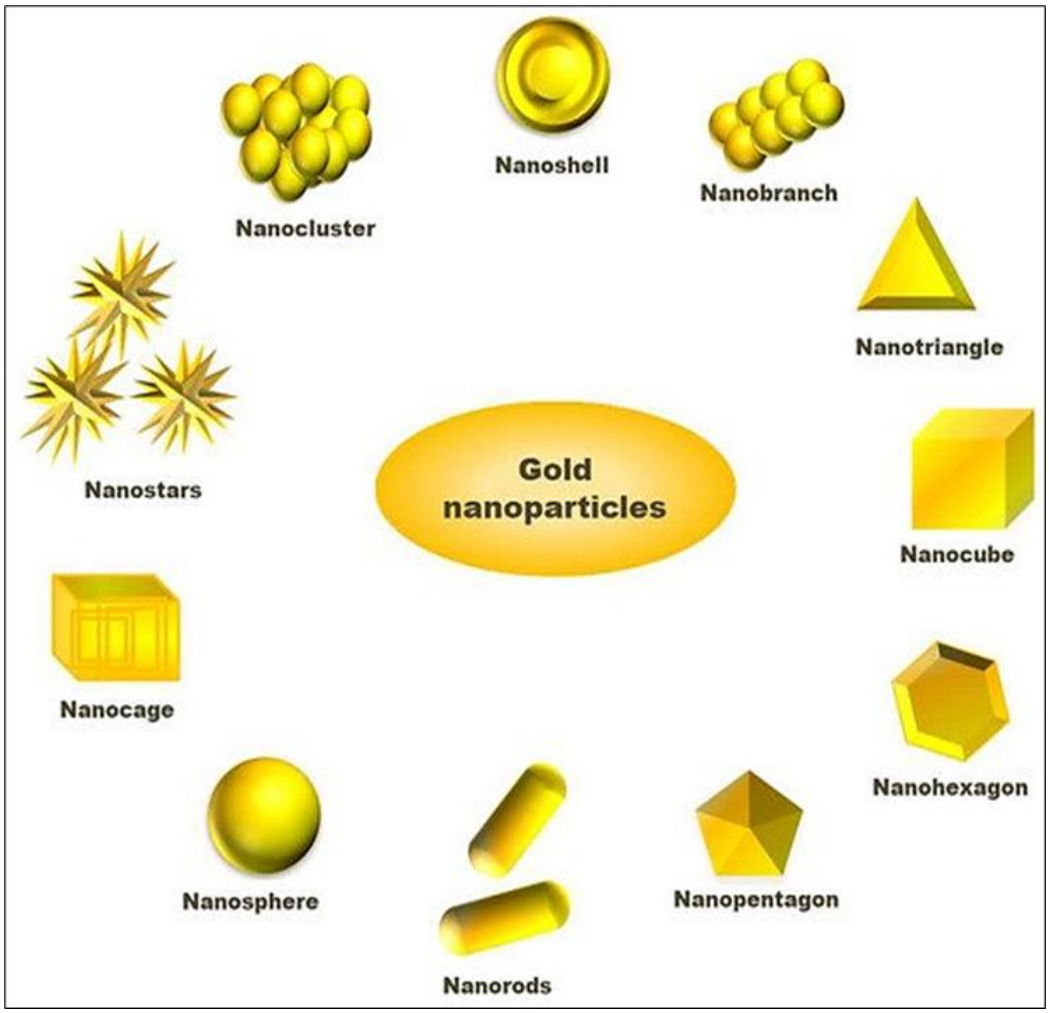

Figure 1 Different shapes available for gold nanoparticles. (4)

2. Preparation of gold nanoparticles

Gold nanoparticles (AuNPs) can be prepared through various methods, including the Turkevich and Frens method (12). The method involves mixing 100 mL of 0.1 g/L chloroauric acid (HAuCl4) with 0.7 mL of 10 g/L trisodium citrate, then heating to boiling while stirring continuously for 30 minutes. After cooling, the resulting solution contains AuNPs with sizes ranging from 10-100 nm. The mixed solution's color changed from pale yellow to burgundy during this process, signifying that the gold nanoparticles successfully produced. The parameters of the study for each batch can meticulously regulated to maintain the uniformity of the shape and volume of the gold nanoparticles. The shape and

volume of the synthesized gold nanoparticles can assessed using scanning electron microscopy and ultraviolet (UV)–visible spectroscopic analysis. (13).

2.1. Synthesis of Gold Citrate Nanoparticle

Combine 48 mL deionized water, 100 mL 0.1 M NaOH, and 0.961 mL 13 mM $HAuCl_4$ in a 100 mL round-bottom flask at 95°C under stirring. Quickly add 0.625 mL 0.1 M sodium citrate.

Reaction Progress-
1. Color change: Pale yellow → Colorless (2 min)
2. Colorless → Gray (5 min)
3. Gray → Clear red → Deep red-wine (~30 min)
4. Stir gently for 30 min after color stabilization.

Conditions-
- Temperature: 95°C
- Stirring: Continuous
- Reaction time: ~60 min(14).

2.2. Synthesis and characterization of Au-NCs

-Mix 1.26 μmol lipids (DOPC:MPB PE, 1:1) in chloroform.
-Evaporate solvents under vacuum overnight to form lipid films.
-Rehydrate films in 10 mM bis-tris propane buffer (pH 7.0) with amph-NPs and ovalbumin.
-Sonicate (6W, 30s intervals, 5 min) on ice.
-Add 10 mM $CaCl_2$ to induce fusion.
-Incubate with 1.5 mM DTT (2:1 maleimide:DTT) for 1 h at 37°C.
-Centrifuge, wash, and PEGylate Au-NCs with 2 kDa PEG-SH.

Characterization
1. Dynamic Light Scattering (DLS) for size distribution.
2. UV-vis spectroscopy for gold concentration.
3. Infrared spectrometry (Direct Detect) for lipid concentration.

Purification and Storage
1. Dilute Au-NCs 2x and filter through 200 nm membrane.
2. Centrifuge, wash 3x with deionized water.
3. Store in phosphate-buffered saline (PBS), pH 7.4 at 4°C.

Size Fractionation
1. Use CL4B gravity columns to collect 4 size fractions.
2. Measure Au-NC size distribution, gold concentration, and lipid concentration.

Conditions
- Temperature: 37°C
- pH: 7.0-7.4
- Buffer: Bis-tris propane, PBS (15).

2.3. Chitosan-gold nanoparticles (CO- AUNPs)

Chitosan-gold nanoparticles (CS-AuNPs) are synthesized through a chemical reduction or green synthesis method. Typically,
1. Mix 10 mL of 1% acetic acid with 20 mg of low molecular weight chitosan solution (2 mg/mL) and vortex to ensure total dissolution.
2. Allow the mixture to stand overnight.
3. Filter 2 mL of the resultant solution through a 0.22 μm polyethersulfone syringe filter.
4. Add 1 mL of 10 mM $HAuCl_4{-}3H_2O$ solution and stir vigorously for 30 minutes.
5. Add 0.4 mL of freshly prepared 100 mM $NaBH_4$ cold solution dropwise while stirring, serving as a reducing agent.
6. Continue stirring for a total of 2 hours, observing a rapid color change from yellow to wine-red (16).

2.4. Green Synthesis Method

AuNP green syntheses, which are alternative eco-friendly and biocompatible processes carried out using plant extracts, have recently been extensively reported in the literature. Organic extracts can have different amounts of reducing agents and different chemical compositions, which can change the final product. It is possible to achieve a variety of geometrical sizes and shapes, which will impact the final application and its function. To cause the reduction of cationic gold into AuNPs, a variety of substances, including proteins, enzymes, amines, aldehydes, ketones, carboxylic acids, phenols, flavonoids, and alkaloids, can supply electrons. The concentrations of the metal salt, plant extract, reaction mixture pH, and temperature all affect the final products' characteristics. Commonly the procedure for plant extract preparation includes some extra preliminary step. (17)

Hydrothermal synthesis is the most prevalent approach for making green CDs due to its affordability and simplicity of execution. The thermal-mediated method necessitates the use of autoclave vessels under high pressure, with reaction temperatures ranging from 120–240 °C, and reaction periods of 3–12 hours in a typical synthesis. The definition of green synthesis stipulates using water (hydrothermal) or being organic solvent (solvothermal) such as ethanol.

Microwave synthesis offers the benefit of directly heating reaction mixtures, usually with approximately 800 W of microwave radiation for a short duration of a few minutes Although there are advantages to microwave synthesis, it might be significantly costlier due to the requirement for specialized equipment. Less control over the synthesis parameters has been sacrificed in favor of using standard household microwaves. A quick, low-energy microwave synthesis at 800 W for three minutes, this quick reaction time—60–240 times faster than hydrothermal synthesis—highlights the microwaves' improved heating efficiency. By resonating with the vibrational frequencies of molecules, microwaves enable direct and selective heating, in contrast to hydrothermal synthesis, which depends on conductive heat transfer. Thus, a microwave reaction is considered finished before there is a noticeable shift in the temperature of an One achieves equivalent hydrothermal synthesis. (18)

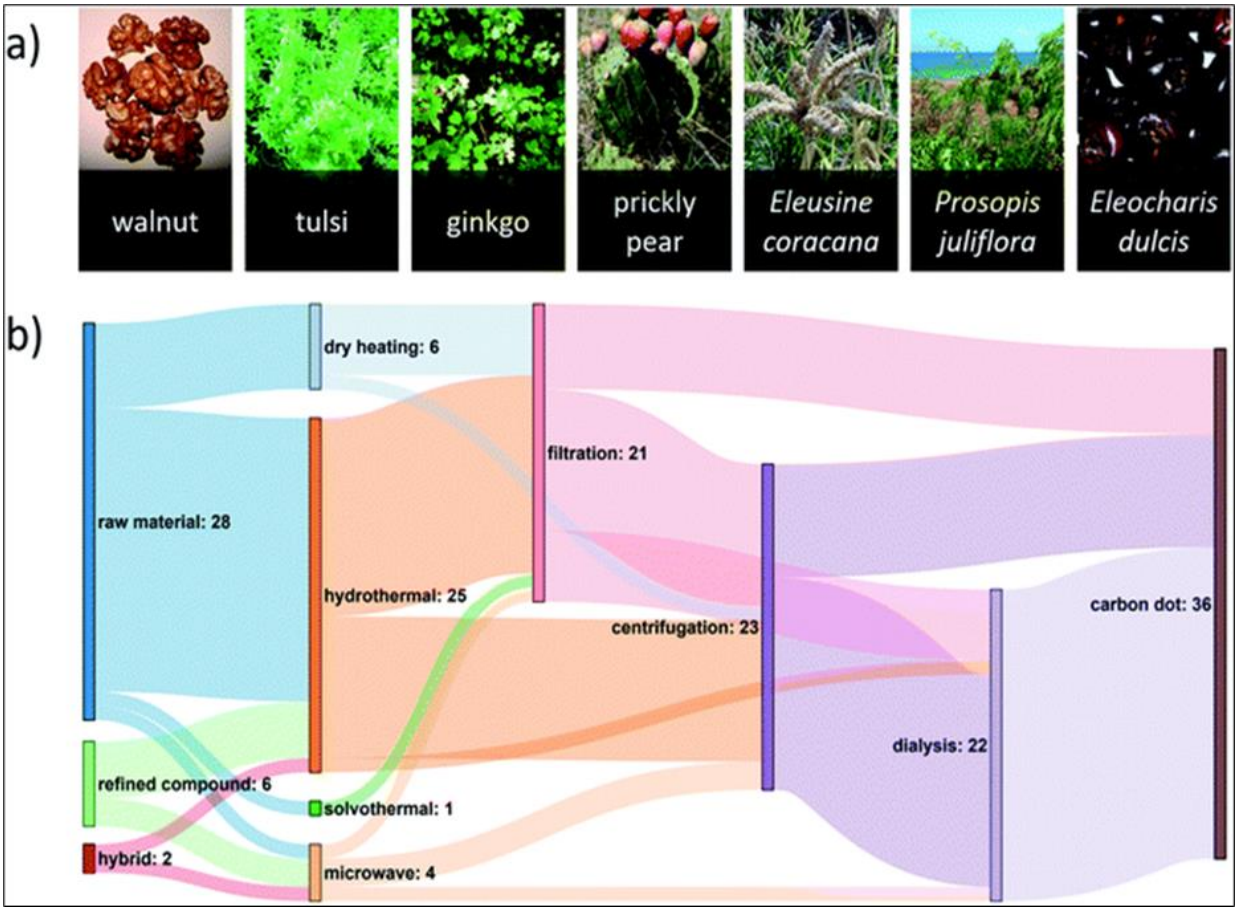

Figure 2 (a) A diverse set of locally sourced renewable precursors can be used for the green synthesis of Carbon dots (CDs). (b) Sankey diagram showing the number of green-synthesized CD publications reporting various pathways from carbon source to CD. (**18**)

3. Properties and Characterization of Gold Nnoparticles

3.1. Plasmonic AuNPs (19,20)

When AuNPs interact with light, the metal's conduction electrons are propelled into collective oscillations known as localized SPRs (LSPRs) by the incident electric field. This is when the SPR effect happens. Electromagnetic fields produced by LSPRs on the surface of the nanostructure can have local field intensities that are orders of magnitude higher than the incident field. Biomedical imaging and therapy can be directly impacted by the enhancement of AuNPs' radiative and nonradiative properties by electromagnetic fields.

3.2. Physicochemical characterization AuNPs (21)

"Optimal particle sizes for biomedical applications of gold nanoparticles (AuNPs), such as drug delivery systems and imaging, range from 10 to 150 nm. Utilizing the developed model, we identified specific experimental conditions for synthesizing AuNPs within this size range: 500 μg/mL melanin, pH 6, and 1.5 mM chloroauric acid (HAuCl4). To monitor the reduction of metal ions, we employed visual observation and colorimetric analysis. Following incubation at 50 °C for 24 hours, the reaction mixture exhibited a distinct purple coloration, indicative of AuNP formation. Conversely, control samples consisting of pure pyomelanin and HAuCl4 did not display any color change under identical conditions.

3.3. Dynamic light scattering and transmission electron microscopy (22)

The characterization of nanoparticles and aggregates entails the assessment of hydrodynamic diameter and surface charge via dynamic light scattering (DLS) and zeta potential measurements utilizing a ZetaPALS instrument (Brookhaven Instruments Corporation). This process involves a two-step procedure, wherein 40 μL of nanoparticle solution is diluted to 1.2 mL with 1 mM KNO3, and UV absorption spectra are subsequently recorded using a GE Lifesciences' Ultrospec 3000pro spectrophotometer. Furthermore, transmission electron microscopy (TEM) is employed to visualize aggregates, involving the deposition and drying of 4 μL aggregate solution on a formvar-stabilized 200/300 mesh copper-carbon grid (Ted Pella), followed by high-resolution TEM imaging using a FEI Tecnai 12 Twin transmission electron microscope.

4. Application of Gold nanoparticles

4.1. AuNPs as sensors for probing and imaging tumor cells (23)

Due to their robust visible light interaction, AuNPs are promising candidates for labeling applications. Gold has the capacity to both absorb and scatter visible light because free electrons in gold atoms are excited to a state of collective oscillation known as surface plasmon resonance (SPR) when exposed to light. Because of their ability to scatter light optically, AuNPs are aimed and gathered at the site of interest in labeling applications, allowing for the visualization of the area being studied. Phase contrast optical microscopy, dark field microscopy, photothermal imaging, and photoacoustic imaging are then possible methods for detecting AuNPs. Furthermore, transmissive electron microscopy still favors AuNPs for immuno-staining and visualization at the ultrastructural level due to their high atomic weight.

4.2. Multifunction gold nanoparticles (24)

Due to their distinctive optical characteristics, such as their resonance light scattering and strong absorption band in the UV-visible range, gold nanoparticles are especially appealing for use in analytical applications. The coherent oscillation of conduction electrons caused by the interacting electromagnetic field is the physical source of the light absorption by gold nanoparticles. Due to the high surface area to volume ratio of nanoparticles, the dielectric (refractive index) nature of their interface with the local medium has a significant impact on the plasmon frequency, which can alter the dispersions' color.

4.3. Testing of catalytic activity of the palladium/gold dried bacteria (25)

"The catalytic activity of palladium-gold-decorated bacteria (2.5% Pd/2.5% Au, w/w) is evaluated using a 50 mL Parr 4592 batch reactor. This reactor is loaded with 50 mL of benzyl alcohol and 180 mg of catalyst, sealed, and heated to 90°C. Once the reactor reaches the desired temperature, air is introduced to establish a 6 bar pressure, maintaining a continuous flow regime. Samples are periodically withdrawn via a sample valve, filtered (0.2 μm), and compared to a commercial standard using gas chromatography-mass spectrometry (GC-MS; Fisons GC8000/MD800)

The incorporation of gold nanoparticles (AuNPs) in palladium-gold-decorated bacteria catalysts enables enhanced catalytic activity for benzyl alcohol oxidation. This is demonstrated through a 50 mL Parr 4592 batch reactor evaluation, where 2.5% Pd/2.5% Au (w/w) decorated bacteria exhibit improved conversion rates and selectivity. The optimized reaction conditions involve heating to 90°C, maintaining 6 bar pressure, and continuous air flow. Periodic sampling and GC-MS analysis reveal significant improvements in reaction yields. This AuNP-enhanced biocatalyst has potential applications in: 1) Fine chemical synthesis, 2)Biomedical research, 3)Fuel cell development.

5. Biomedical applications

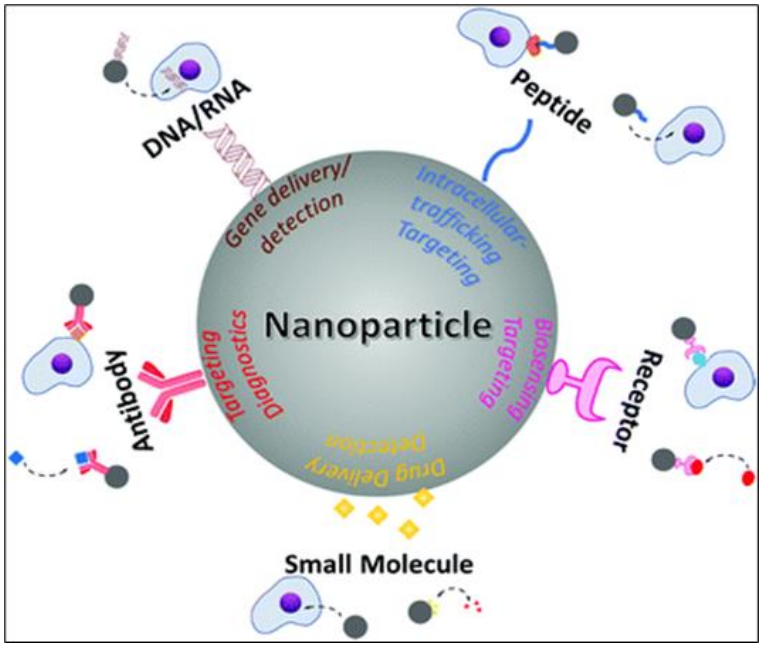

Figure 3 Biomedical applications of nanoparticles through conjugation with various active moieties including DNA/RNA, peptides, receptors, antibodies, and small molecules. (26)

5.1. Cell Culture (27,28)

To prepare cell cultures for gold nanoparticles (AuNPs), the cell culture protocols utilize the following cell lines: SKBR3 (ATCC HTB-30), HEp-2 (ATCC CCL-23), Panc1, and 4911. These cell lines are cultured under standard conditions, including incubation at 37°C with 5% CO2 and 95% humidity, maintaining suitable cell lines in appropriate culture media: EMEM for HEp-2, McCoy for SKBR3, and RPMI for Panc1 and 4911. Supplements are added to the media, including 1% penicillin-streptomycin, 5% fetal bovine serum (FBS) for SKBR3 and HEp-2, and 10% FBS and 1% L-glutamine for Panc1 and 4911. For cell growth and seeding, SKBR3 and HEp-2 are plated at a density of 8,000 cells/well, while Panc1 and 4911 are maintained at 60-70% confluency in 60 mm dishes. These protocols are based on established methods.

Gold nanoparticles (AuNPs) are utilized in various biomedical applications, including cancer research, diagnostics, and therapy, through cell culture protocols employing specific cell lines. The SKBR3, HEp-2, Panc1, and 4911 cell lines are cultured under standardized conditions, facilitating AuNP interactions with cancer cells.

5.2. Cell Morphology and viability (29)

Glioblastoma cells (~5×103) are seeded into flat-bottom well plates and incubated for 24 hours at 37°C. The cells are then treated with either rHDL or rHDL-AuNP overnight, along with 10% LPDS. Following treatment, cell morphology is analyzed using bright-field microscopy (Leica DM IRB inverted phase contrast microscope).

To assess cell viability, the MTT test (Sigma-Aldrich) is employed. Cells are exposed to rHDL-AuNP at concentrations ranging from 0.1 to 100 µg/mL for 24 hours at 37°C. MTT dye is then added and incubated for an additional 4 hours. After aspirating the media, formazan crystals are dissolved using a solubilizing solution (20% SDS/50% dimethylformamide) at pH 4.7. Absorbance is measured at 570 nm using a Thermo Fisher Scientific Varioskan TM spectrophotometer. Gold nanoparticles (AuNPs) are utilized in this study to enhance glioblastoma cancer research,

particularly in targeted therapy and diagnostic applications. The incorporation of AuNPs into reconstituted high-density lipoprotein (rHDL-AuNP) enables targeted delivery of therapeutic agents to glioblastoma cells, potentially improving treatment efficacy. Additionally, AuNPs' unique optical properties facilitate enhanced imaging contrast, allowing for more accurate assessment of cell morphology and viability.

5.3. Classification of the Lung Cancer histology with Gold nanoparticle sensors (30)

Lung cancer (LC) diagnosis has been revolutionized by the development of gold nanoparticle (GNP) sensors. Recent studies have demonstrated a strong correlation between volatile organic compounds (VOCs) detected by gas chromatography-mass spectrometry (GC-MS) and the organic ligands of GNP sensors.

GNP sensors have shown remarkable ability in distinguishing LC from non-cancerous cell lines. The decanethiol-coated GNP sensor (sensor 1) exhibited superior discrimination due to its structural resemblance to decanal, a key VOC in LC cell lines. Van der Waals interactions between decanal and decanethiol ligands facilitate this detection.

Multiparametric Sensing- To differentiate non-small cell lung cancer (NSCLC) from small cell lung cancer (SCLC), two additional GNP sensors were employed: hexanethiol (sensor 2) and butanethiol (sensor 3). These sensors detected benzene-1,3-bis(1,1-dimethylethyl) and acetophenone, VOCs that play significant roles in LC subtype separation.

Improved Sensitivity- Replacing butanethiol-GNPs with 2-mercaptobenzoxazole GNPs enhanced adenocarcinoma and squamous cell carcinoma differentiation. This advancement highlights the potential of GNP sensors in precise LC classification.

6. Mechanism of Action

6.1. Mechanisms of ferroptosis

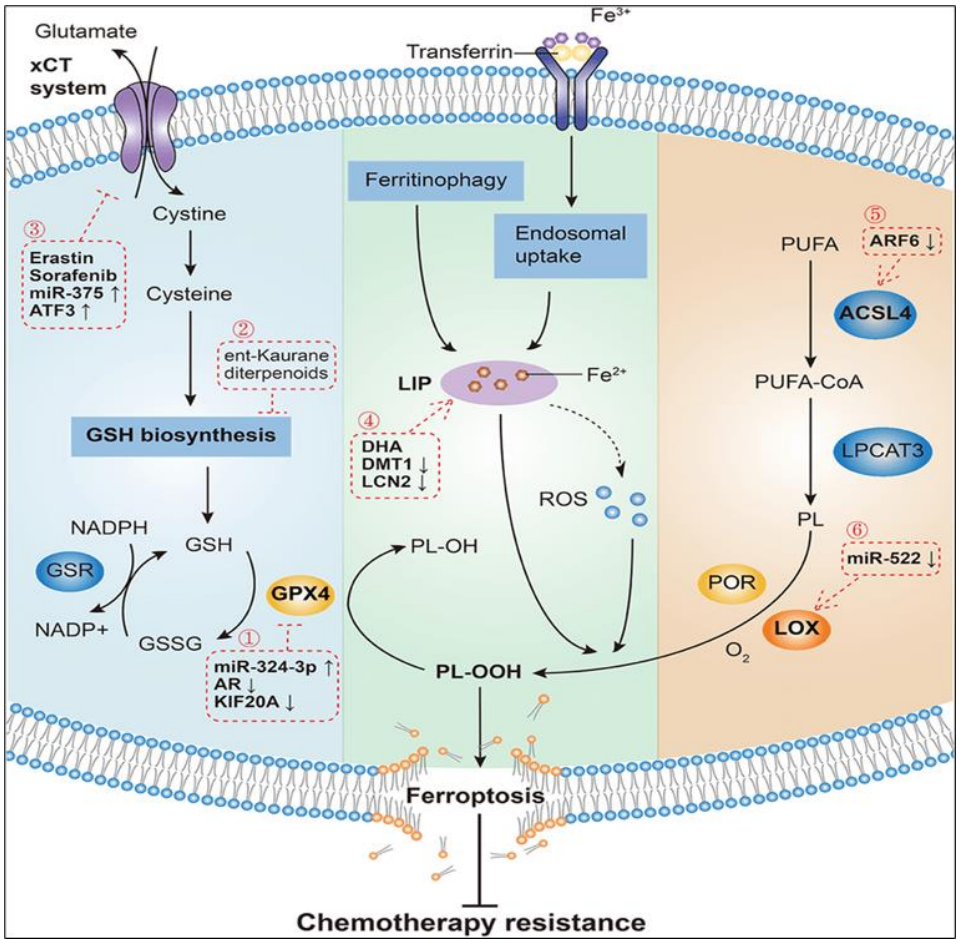

Figure 4 Mechanisms governing ferroptosis and reversing chemotherapy resistance. (31)

Ever since the GPX4-centered mechanisms of ferroptosis were identified in 2014, more research has been done to find new mechanisms regulating the process (31). Regulation of ferroptosis by nanotechnology for enhanced cancer immunotherapy (32). The pathways not dependent on GPX4 have also been identified. These investigations have provided a strong theoretical foundation for the initiation of ferroptosis, which can be broadly categorized into three pathways: the iron metabolism pathway, the lipid metabolism pathway, and the canonical GPX4-regulated pathway (31). Defense mechanisms against antioxidants: Following the identification of ferroptosis, scientists discovered that glutathione peroxidase 4 (GPX4) was a common mediator for 12 small molecules that cause ferroptosis. By converting intracellular PLOOH to innocuous phosphatidyl alcohol (PLOH), GPX4 can stop lipid peroxides from building up. Each time this reaction occurs, two molecules of glutathione (GSH) must be consumed (33). A novel autophagic substrate that increased ferroptosis resistance was SLC40A1. SLC40A1 degradation during ferroptotic cancer cell death requires autophagy. The important autophagy receptor SQSTM1 can be knocked down to reverse the downregulation of the SLC40A1 protein, according to researchferroptosis (34).

6.2. LIPID Metabolism (35,36,37)

Gold nanoparticles can interact with the biochemical processes involved in ferroptosis, potentially influencing cell death.

Following step describes the biochemical link between lipid metabolism and ferroptosis, a form of cell death:

- Polyunsaturated fatty acids (PUFAs) are prone to oxidation due to their molecular structure, making them essential for ferroptosis.
- Phospholipids in cell membranes incorporate PUFA chains, increasing vulnerability to oxidation.
- Specific enzymes (LPCAT3 and ACSL4) facilitate this incorporation, and deleting these genes can prevent ferroptosis.
- Research findings show varying levels of 4-HNE, ACSL4, and LPCAT3 in tumor tissues, suggesting a connection between fatty acid metabolism and cancer progression.
- Monounsaturated fatty acids (MUFAs), produced by stearoyl-CoA desaturase1 (SCD1), can competitively bind to cell membranes and prevent ferroptosis.
- The interaction between PUFAs, ACSL4, LPCAT3, and lipoxygenase (LOXs) leads to the formation of lipid hydroperoxides, inducing ferroptosis.

7. Limitations

While AuNPs are highly advantageous as drug carriers, their primary barrier to wider adoption is safety. Although more research has shown toxicity, the bulk of reports have suggested that AuNPs are safe. Size, shape, conjugated materials, nucleic acids, dosage, and biodegradability can all have an impact on toxicity. Compared to nanospheres, nanostars are less toxic. Furthermore, ligand types and surface charges may have an impact on toxicity. For instance, when it comes to Gram-negative and -positive bacteria (Shewanella oneidensis and Bacillus subtilis, respectively), cationic and polyelectrolyte-wrapped AuNPs are more toxic than electronegative and anionic 3-mercaptopropionic acid- and cationic 3-mercaptopropylamine-wrapped AuNPs. These contentious results necessitate the development of more thorough, uniform standards for assessing AuNP toxicity (38).

8. Advantages and Future Directions

- Increasing the stability and dispersibility of AuNPs by conjugating molecules to their surface, which inhibits precipitation and aggregation.
- Altering optical characteristics, as AuNPs have special optical qualities that can be modified for use in optical imaging and therapy, such as controlling the wavelength, intensity, and direction of light absorption and scattering.
- Improving targeting, which is accomplished by changing targeting ligands on the surface of AuNPs to precisely target particular cells, tissues, or biological molecules.
- Increasing biocompatibility, which is realized by changing molecules on the surface of AuNPs to reduce toxicity for use in the biomedical field diagnosis and treatment.
- Improving drug delivery capacity by altering medications on AuNPs' surface, which can also raise therapeutic efficacy and lower adverse drug reactions.
- Scientists can now investigate their concepts in the biomedical field thanks to nanotechnology (39).
- After parenteral administration, it is simple to modify the particle size and surface properties of nanoparticles to achieve both passive and active drug targeting (40).
- Systems for delivering drugs mediated by gold nanoparticles offer numerous benefits over alternative nanocarriers and traditional medications (41).

- Gold-cored nanoparticles have been applied for many years. There are several methods for creating nanoparticles, the simplest of which is to reduce gold salts with a reducing agent present (42).
- Compared to conventional drugs and other nanocarriers, gold nanoparticle-mediated drug delivery systems offer numerous advantages (43).

9. Conclusion

Gold nanoparticles (AuNPs) have shown significant potential in biomedical applications, particularly in cancer research, diagnostics, and therapy. AuNPs' unique optical, electrical, and photothermal properties make them ideal for sensing, imaging, and targeted therapy. The development of AuNP-mediated drug delivery systems has improved targeting efficiency, diagnostic sensitivity, and therapeutic outcomes. Understanding the mechanisms of ferroptosis and lipid metabolism is crucial for enhancing cancer treatment and overcoming chemotherapy resistance. AuNP-based sensors have demonstrated remarkable ability in distinguishing lung cancer from non-cancerous cell lines. Nanotechnology has emerged as a promising tool for regulating ferroptosis and enhancing cancer immunotherapy.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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