

REVIEW ARTICLE

Gold Nanoparticles: A Critical Review of Synthetic Strategies, Structure–Property Correlations, and Emerging Technological Applications

Rajniket R Dushing, Ramnath A Pawar*

ABSTRACT: Gold nanoparticles (AuNPs) have established themselves as a cornerstone of modern nanoscience, captivating researchers with their remarkable optical, electronic, and catalytic properties, which are primarily dictated by the localized surface plasmon resonance. This review provides a critical and comprehensive analysis of the synthetic landscape for AuNPs, tracing the evolution from foundational methods like the Turkevich and Brust-Schiffrin approaches to contemporary advancements in seed-mediated, physical, and green biological syntheses. A central focus is placed on how the choice of synthesis method dictates critical physicochemical parameters, including size distribution, shape anisotropy, surface chemistry, and colloidal stability, which in turn define the nanoparticle's functional potential. The review then navigates through the expanding application space of these engineered nanomaterials, emphasizing their transformative roles. In the biomedical arena, we examine their utility as theranostic agents, highlighting their application in targeted drug delivery, photothermal therapy, and advanced bioimaging. The unique catalytic capabilities of AuNPs are discussed in the context of facilitating efficient redox reactions for chemical synthesis and environmental remediation. Furthermore, we explore their integration into high-sensitivity sensing platforms for environmental pollutants and biomarkers, as well as their growing importance in next-generation electronic devices, including flexible conductors, printable inks, and molecular-scale electronic components. By synthesizing current knowledge and identifying critical gaps, this review aims to provide a holistic understanding of the challenges and opportunities that define the future trajectory of gold nanoparticle research.

Keywords: Gold Nanoparticles, Plasmonics, Seed-Mediated Synthesis, Colloidal Stability, Nanotheranostics, Catalysis.

Received: 13 November 2025; Revised: 02 January 2026; Accepted: 28 January 2026; Published Online: 05 February 2026

1. INTRODUCTION

The genesis of nanotechnology, though a modern scientific discipline, can be traced back to empirical practices from centuries past. Early artisans, such as those in 9th century Mesopotamia, unknowingly manipulated materials at the nanoscale to create a lustrous, iridescent effect on pottery, a

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phenomenon now understood to arise from the presence of metallic nanoparticles [1]. A significant scientific leap occurred in 1857 when Michael Faraday systematically investigated the optical properties of finely divided gold, observing that its colloidal solutions exhibited a striking ruby-red color distinct from the bulk metal [2]. This work laid the foundational principles for the study of colloidal gold. Building upon this, Richard Zsigmondy made critical advancements by developing the ultramicroscope, enabling direct visualization of nanoparticles and their characterization. His work culminated in the introduction of the seed-mediated method, a technique that remains a cornerstone for synthesizing various nanoparticles today [3,

4]. Furthering the understanding of colloidal behavior, Theodor Svedberg invented the ultracentrifuge, providing conclusive evidence that the motion of macromolecules and colloids is governed by their size and shape [5].

These early investigations collectively established the groundwork for what has now become a significant subdiscipline: the chemistry and physics of gold nanoparticles (AuNPs) [6]. The enduring fascination with AuNPs stems from their unique, size-dependent properties, which diverge dramatically from those of bulk gold. At the nanoscale, gold is no longer merely an inert, lustrous metal but a reactive, colorful, and functional material. This size-dependent behavior manifests as a high surface-area-to-volume ratio, distinct electronic structures, and the phenomenon of localized surface plasmon resonance (LSPR), which is responsible for their intense optical absorption and scattering [2, 7]. These unique attributes have positioned AuNPs as invaluable components across a vast array of fields, from medicine to electronics [6-9].

The synthesis of AuNPs is primarily achieved through physical, chemical, or biological routes, with chemical reduction being the most prevalent due to its versatility and control [9]. This ability to tailor their size, shape, and surface chemistry is what underpins their functionality. For instance, their exceptional biocompatibility and ease of surface functionalization have propelled their use in diverse biomedical applications, including targeted drug delivery, photothermal therapy for cancer, advanced biosensing platforms, clinical diagnostics, and high-resolution optical and photoacoustic imaging [1, 10-12]. Their surface plasmon resonance also makes them ideal for sensitive chemical and biological sensing. Concurrently, their catalytic activity, particularly in oxidation and reduction reactions, is exploited in chemical synthesis and environmental remediation [6, 9, 13]. In the realm of electronics, AuNPs serve as critical components in conductive inks for flexible circuits and as nanojunctions in next-generation memory devices [6, 13].

Modern research is increasingly focused on moving beyond simple spherical nanoparticles. The current frontier involves the structure-divergent synthesis of complex anisotropic architectures such as nanorods, nanocages, nanostars, and silica-coated nanoshells [1, 13]. Each of these morphologies exhibits unique and tunable plasmonic properties, enabling applications that range from enhanced imaging contrast to targeted photothermal therapy. The profound interest in AuNPs is ultimately driven by the fact that their properties are not merely a scaled-down version of the bulk material but are a consequence of quantum effects, electromagnetic confinement, and the dominance of surface atoms, leading to behaviors such as a transition from metallic to semiconducting states in ultra-small particles [6]. This remarkable convergence of synthetic control and emergent properties continues to make gold nanoparticles a central focus of nanoscience research.

2. HISTORICAL OVERVIEW OF AU NANOPARTICLE SYNTHESIS METHODS

The history of gold nanoparticle synthesis is a compelling narrative of scientific evolution, marked by a progressive shift from empirical observation to a deep, mechanism-driven understanding of nanoscale chemistry. The journey formally began in the mid-19th century with Michael Faraday. In 1856, Faraday published his seminal work on the preparation and properties of colloidal gold, demonstrating the first systematic chemical reduction of a gold salt (HAuCl_4) to produce stable, ruby-red solutions [14]. His insight was revolutionary: he recognized that the observed color was an intrinsic property of the finely divided gold particles themselves, not a chemical impurity, thus laying the conceptual foundation for colloid science.

The next major paradigm shift occurred over a century later with the work of Turkevich and his colleagues. In 1951, they introduced a now-classic method that used trisodium citrate to both reduce chloroauric acid and stabilize the resulting nanoparticles [4]. This aqueous synthesis was a breakthrough because it was simple, reproducible, and produced relatively monodisperse spherical particles. The citrate ions acted as a dual-function agent: a mild reductant and an electrostatic stabilizer, preventing aggregation. This method was further refined in 1973 by Frens, who demonstrated that the size of the resulting nanoparticles could be precisely controlled by simply varying the citrate-to-gold molar ratio [15]. This discovery provided researchers with a simple tool to tune the nanoparticle diameter from about 5 to 150 nm, establishing a foundation for countless future studies.

While the Turkevich-Frens method was ideal for producing spherical particles in water, a new frontier opened in 1994 with the Brust-Schiffrin method [16, 17]. This innovative two-phase synthesis allowed for the creation of ultra-small gold nanoparticles, typically 1 to 6 nm in diameter, that were stable in organic solvents. The process involved transferring gold ions into an organic phase using a phase-transfer agent, followed by reduction with sodium borohydride and immediate capping with a thiol molecule. This was transformative because it enabled the production of extremely stable, functionalized nanoparticles that could be redissolved and manipulated in organic media, opening the door to self-assembly studies and early nanoelectronic applications.

The late 1990s and early 2000s witnessed a surge in interest in controlling not just size, but also shape. The seed-mediated growth method, pioneered by Murphy and colleagues, elegantly decoupled the process of nucleation from growth [18]. Small, pre-formed gold "seeds" were introduced into a growth solution containing gold salt, a mild reducing agent (ascorbic acid), and a shape-directing surfactant like cetyltrimethylammonium bromide (CTAB). This approach allowed the seeds to grow anisotropically. A pivotal moment came in 2003 when Nikoobakht and El-Sayed demonstrated that the addition of silver ions to this growth solution enabled the high-yield, reliable synthesis of gold nanorods [3]. This work was a landmark achievement, as it marked the onset of deliberate shape engineering, enabling the tuning of the plasmon resonance across the

visible and near-infrared spectrum by simply adjusting the aspect ratio of the nanorod.

Concurrently, physical methods emerged as a powerful alternative for producing high-purity, surfactant-free nanoparticles. The development of laser ablation in liquids allowed for the generation of nanoparticles by focusing a pulsed laser onto a gold target submerged in a liquid [17]. This technique produces nanoparticles in the absence of any chemical reducing agents, resulting in a pristine surface ideal for fundamental studies in catalysis and for applications where surface chemistry is critical. Similarly, sonochemical methods, which use high-intensity ultrasound to generate extreme conditions and reducing radicals, offered another route to clean nanoparticles [18].

The past two decades have been characterized by a drive towards greater precision, scalability, and sustainability. The 2010s saw the rise of "green" synthesis using plant extracts and microorganisms, which provided a biocompatible and environmentally benign alternative to traditional chemical methods [19]. Concurrently, there was a growing emphasis on surface programmability, using polymers, DNA, and polyethylene glycol (PEG) to impart biocompatibility and specific biorecognition capabilities. To address the challenge of industrial reproducibility, researchers began employing microfluidic continuous-flow reactors, which offer superior control over mixing and reaction conditions compared to traditional batch processes [19].

Today, the field is defined by an unprecedented level of control. Current research focuses on kinetic precision, utilizing photochemical and plasmon-induced reduction pathways to achieve spatiotemporal control over synthesis [20]. The integration of artificial intelligence and machine learning is beginning to optimize synthetic protocols,

predicting reaction conditions that yield desired morphologies with high reproducibility. This modern era positions gold nanochemistry not just as a synthetic endeavor but as a cornerstone technology for advanced applications in sensing, biomedicine, catalysis, and energy-relevant nanodevices [17].

3. SYNTHESIS METHODS

The synthesis of gold nanoparticles (AuNPs) can be broadly classified into physical, chemical, and biological approaches, each operating on distinct principles and requiring specific environmental conditions. Physical methods, such as laser ablation and evaporation-condensation techniques, typically involve high-energy processes and yield nanoparticles with high purity, often free from chemical contaminants [17]. Chemical synthesis methods, which are the most widely employed, rely on the reduction of gold salts in solution and offer exceptional control over particle size, morphology, and surface characteristics [21, 22]. In contrast, biological or green synthesis utilizes microorganisms, enzymes, or plant extracts as both reducing and stabilizing agents, providing an eco-friendly alternative [9]. Due to the fundamental differences among these synthesis routes, the resulting AuNPs exhibit diverse physicochemical properties, which in turn determine their suitability for various applications ranging from catalysis and electronics to biomedical imaging and sensing [9]. Figure 1 provides a schematic overview of these three primary synthesis categories, illustrating their distinct mechanisms, environmental requirements, and the resultant nanoparticle characteristics.

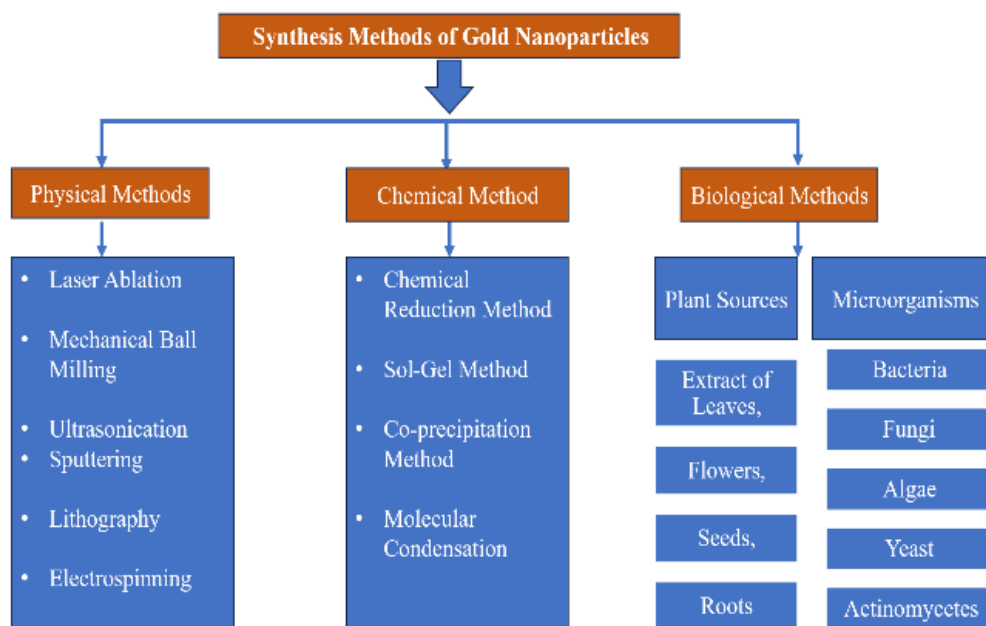


Fig. 1. Schematic representation of the three primary routes for gold nanoparticle synthesis: physical, chemical, and biological methods. Each approach differs in its underlying mechanism, required conditions, and the key properties of the resulting nanoparticles.

3.1. Chemical Methods

Chemical synthesis remains the most versatile and widely adopted approach for producing AuNPs, offering precise control over size, shape, and surface functionality. A diverse array of chemical methods exists, each with its own principle, parameters, and conditions. These include the classic Turkevich method [23], the Brust-Schiffrin two-phase method [24], the aqueous synthesis of tiopronin-capped nanoclusters [25], paper-based UV dosimeter fabrication via solid-state photochemical reduction [26], seed-mediated synthesis using chiral amino acids and peptides [27], shape-directing agent-based synthesis [28], and surfactant-free colloidal synthesis at room temperature [29]. Figure 2 illustrates the generalized step-by-step approach common to many chemical reduction methods, highlighting the sequential addition of precursor, reductant, and stabilizer under controlled conditions.

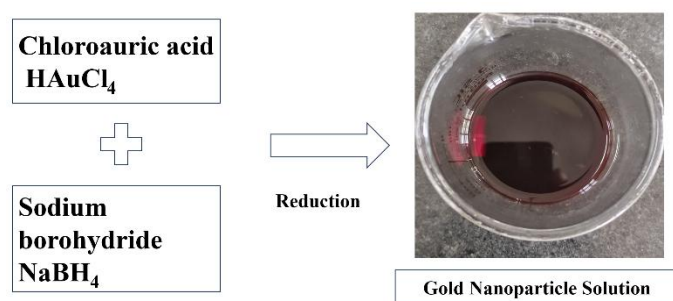


Fig. 2. A generalized step-by-step schematic of gold nanoparticle synthesis via chemical reduction, showing the key stages from precursor dissolution to nanoparticle formation and stabilization.

The Turkevich method, first reported in 1951, is one of the oldest and most reliable routes to spherical AuNPs [4, 23]. In this method, a defined volume of chloroauric acid (HAuCl_4) solution is added to deionized water and brought to a boil under continuous stirring. Once stable boiling is achieved, a solution of trisodium citrate is introduced. The citrate acts as both a reducing agent and an electrostatic stabilizer. The reaction is maintained at boiling with constant stirring to ensure homogeneous nucleation and controlled growth. The final particle size, typically ranging from 10 to 50 nm, is governed by the citrate-to-gold molar ratio, temperature, and mixing conditions. The resulting quasi-spherical AuNPs exhibit good colloidal stability and tunable optical properties, making them highly suitable for therapeutic and diagnostic applications [23, 30].

In the aqueous synthesis of tiopronin-capped gold nanoclusters, chloroauric acid dissolved in water provides Au^{3+} ions, which first interact with tiopronin, a thiol-containing ligand. Upon addition of sodium hydroxide, the thiol ($-\text{SH}$) groups of tiopronin are deprotonated to form reactive thiolate ($-\text{S}^-$) species, enabling strong coordination with Au^{3+} ions. Subsequent reduction with sodium

borohydride (NaBH_4) rapidly converts Au^{3+} to metallic Au^0 , leading to the formation of ultrasmall gold nanoclusters. The tiopronin molecules bind tightly to the gold surface through $\text{Au}-\text{S}$ bonds, effectively capping and stabilizing the nanoclusters, preventing aggregation, and controlling their size at the sub-2 nm scale. This dialysis-free synthesis yields nanoparticles with stable nucleation, photoluminescence, and controllable hydrodynamic size, properties that are particularly valuable for drug delivery, biomedical applications, and biomolecule detection [25].

The seed-mediated synthesis using chiral amino acids and peptides represents an advanced strategy for producing nanoparticles with defined chiral morphology. In this approach, preformed octahedral gold seeds serve as nucleation templates for anisotropic growth. Chiral agents such as L-glutathione (L-GSH) or D-glutathione (D-GSH) are introduced as structure-directing and surface-selective ligands. These chiral molecules preferentially adsorb onto specific crystallographic facets of the seeds [27, 31]. The reaction is carried out at room temperature and allowed to proceed for approximately 8 hours, during which controlled deposition of gold occurs. The final morphology, size uniformity, and chirality of the gold nanostructures are governed by the optimized concentrations of seeds and peptides, enabling enantioselective growth and well-defined colloidal stability. This method yields 432-symmetric helicoid III nanoparticles with well-defined chiral morphology, characterized by a high g-factor of approximately 0.2, a tunable circular dichroism (CD) peak, and consistent reproducibility. The chiroptical properties are dependent on seed quality and synthesis optimization, enabling applications in chiral sensing, polarization control, and biomedical diagnostics [26].

A notable advancement in simplifying synthetic protocols is surfactant-free colloidal synthesis. This method yields quasi-spherical gold nanoparticles with sizes ranging from 5 to 22 nm. Notably, the smallest nanoparticles, around 5 nm in diameter, exhibit the highest electrochemical activity, a feature attributed to their larger surface-to-volume ratio and increased number of active surface sites. By eliminating surfactants, this method enables a clear and systematic evaluation of size-dependent catalytic effects without the interference of surface-bound capping agents. Consequently, the synthesized AuNPs are exceptionally well-suited for applications in alcohol electro-oxidation reactions, green catalytic processes, and fundamental studies on size effects in electrocatalysis [29].

The classic Turkevich method using trisodium citrate remains a cornerstone of nanoparticle synthesis due to its simplicity and reliability. In this approach, citrate acts as both a reducing and stabilizing agent. It initially forms a transient complex with Au^{3+} ions, reducing them to Au^+ species, followed by complete reduction to metallic Au^0 under boiling conditions [32]. This dual functionality enables controlled nucleation and growth, resulting in highly stabilized, predominantly spherical AuNPs with tunable sizes ranging from approximately 5 to 150 nm by simply adjusting the citrate-to-gold ratio and reaction conditions.

Table 1. Chemical synthesis methods of gold nanoparticles and the commonly used gold precursors, reducing agents, and stabilizing/capping agents.

Chemical Synthesis Method	Gold Precursor	Reducing Agent	Stabilizing / Capping Agent	Typical Size (nm)	Remark
Turkevich method (citrate reduction)	HAuCl ₄ ·3H ₂ O	Trisodium citrate	Citrate ions (self-capping)	10–50	Simple, aqueous, produces spherical and fairly monodisperse AuNPs
Brust–Schiffrin method	HAuCl ₄	NaBH ₄	Alkanethiols (e.g., dodecanethiol)	1–5	Highly stable, organic-phase synthesis, small-sized nanoparticles
Seed-mediated growth	HAuCl ₄	Ascorbic acid (mild)	CTAB, PVP	10–200	Enables anisotropic shapes (nanorods, stars, bipyramids)
Polyol method	HAuCl ₄	Ethylene glycol	PVP	5–100	High-temperature process, good size and shape control
Photochemical reduction	HAuCl ₄	UV/visible light (photo-reduction)	Citrate, PVP	5–60	No chemical reducing agent, spatial and temporal control
Microemulsion method	HAuCl ₄	NaBH ₄	Surfactants (AOT, CTAB)	2–20	Narrow size distribution, confined growth environment
Electrochemical reduction	Au salt or Au electrode	Electrochemical electrons	Tetraalkylammonium salts	5–20	High purity, no chemical reducing agents
Sonochemical method	HAuCl ₄	Radicals from acoustic cavitation	PVP, citrate	10–100	Rapid synthesis, enhanced nucleation rate

Owing to its simplicity, reliability, and reproducibility, this method is widely employed in nanoparticle synthesis, with extensive applications in biosensing, diagnostics, and optical sensor platforms [30].

Table 1 summarizes the key chemical synthesis methods for gold nanoparticles, detailing the gold precursors, reducing agents, stabilizing or capping agents, and the typical size ranges and remarks for each approach. This table provides a concise overview of the diversity and capabilities of chemical synthesis routes.

3.2. Physical Methods

Physical methods for gold nanoparticle synthesis offer distinct advantages, particularly in producing high-purity nanoparticles without the need for chemical reducing agents or surfactants. These approaches typically involve high-energy processes such as laser ablation, sputtering, or thermal evaporation, which generate nanoparticles through the physical disintegration of a bulk gold source. The resulting nanoparticles often possess pristine surfaces, making them highly suitable for fundamental studies and applications where surface chemistry must be precisely controlled. Among the various physical methods, pulsed laser ablation in liquid (PLAL) has emerged as one of the most versatile and widely investigated techniques.

Figure 3 presents a schematic diagram of the typical experimental setup for PLAL. In this method, high-energy laser pulses are focused onto a bulk gold target submerged in a liquid medium, typically deionized water or an organic solvent. The rapid laser–matter interaction generates a transient, high-temperature plasma plume at the target surface. As this plasma cools and condenses, gold nanoparticles are formed and dispersed into the surrounding liquid [33]. This approach is inherently eco-friendly, as it eliminates the need for chemical reducing agents and stabilizers, and the nanoparticle surface remains ligand-free unless a functionalizing agent is intentionally introduced into the liquid medium.

Using a 1064 nm Nd:YAG laser with ablation times of 15 and 30 minutes, this method produces well-dispersed, spherical AuNPs with average sizes of 5.20 nm and 7.46 nm, respectively [17]. The nanoparticles exhibit excellent biocompatibility and demonstrate strong antibacterial activity, with a remarkably low minimum inhibitory concentration of 1.719 µg/mL against *Staphylococcus aureus*. This potent antibacterial effect, combined with their biocompatibility, makes these PLAL-generated AuNPs highly suitable for applications such as antibacterial coatings in dental implants [17]. Variations in laser wavelength and ablation medium can further tune the nanoparticle properties. For instance, ablation in a microemulsion medium (MEM) using 532 nm and 1064 nm lasers yields smaller

nanoparticles (approximately 8.84 nm) compared to ablation in deionized water (DW), which produces particles around 16.3 nm. These nanoparticles have shown efficacy in photothermal cancer therapy, achieving approximately 43 to 58 percent ablation of MDA-MB-231 cancer cells when irradiated at a concentration of 600 $\mu\text{g/mL}$ [34].

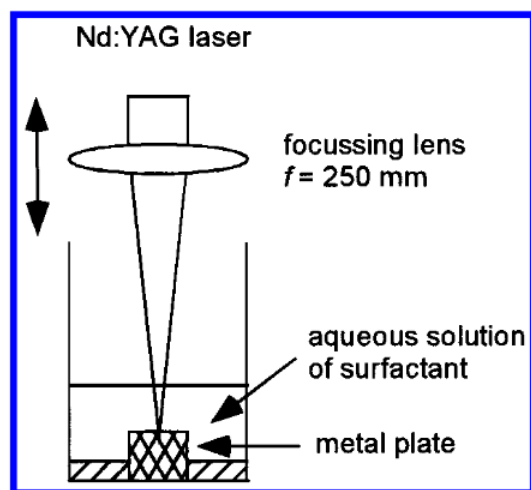


Fig. 3. Schematic diagram of the experimental apparatus for pulsed laser ablation in liquid. High-energy laser pulses are focused onto a gold target immersed in a liquid medium, generating a plasma plume that condenses to form gold nanoparticles. [Reprinted with permission from ref. [17]. Mafuné, F., Kohno, J., Takeda, Y., Kondow, T., & Sawabe, H. (2001). Formation of Gold Nanoparticles by Laser Ablation in Aqueous Solution of Surfactant. *The Journal of Physical Chemistry B*, 105(22), 5114-5120. Copyright © American Chemical Society.]

The PLAL technique has been extended beyond simple nanoparticle synthesis to the fabrication of complex core-shell nanostructures. In the simultaneous ablation approach for core-shell $\text{Au@Fe}_3\text{O}_4$ nanostructures, gold and iron oxide targets are ablated together in a liquid medium, promoting the in situ formation of nanoparticles with a gold core and an iron oxide shell. Using a laser energy of 1200 mJ and a porous silicon substrate, this synthesis yields well-defined core-shell particles with an average size of approximately 25 nm, as confirmed by X-ray diffraction (XRD), photoluminescence (PL), and transmission electron microscopy (TEM) analyses. The resulting nanostructures exhibit tunable optical bandgaps in the range of 2.38 to 2.53 eV and demonstrate a high photodetector responsivity of 0.189 A/W, highlighting their strong potential for advanced photodetector and biosensing applications [6].

A related approach, PLAL-assisted doping, involves irradiating a gold target in a sol-gel medium containing cadmium sulfide (CdS). This process allows for the incorporation of gold species into the CdS matrix during nanoparticle generation. Using a 1064 nm Nd:YAG laser with a pulse energy of 700 mJ at 9 Hz, and varying the number of irradiation pulses between 500 and 2500, gold

species are generated and uniformly doped into the CdS matrix. The resulting spin-coated CdS:Au thin films exhibit reduced crystallite sizes ranging from 6.6 to 9.3 nm and a decreased grain size down to 25.8 nm. The introduction of gold induces a bandgap reduction from 2.39 to 2.33 eV and enhances the nonlinear refractive and absorptive properties of the films. These characteristics make the materials promising candidates for optical modulators, photonic devices, and nonlinear optical applications [6].

Beyond laser-based techniques, other physical methods offer complementary advantages. The coprecipitation combined with ultrasonic spray pyrolysis (USP) approach provides a route to hybrid nanostructures. In this method, Fe_3O_4 nanoparticles are first synthesized via base-induced coprecipitation of Fe^{2+} and Fe^{3+} salts using ammonium hydroxide (NH_4OH), producing a superparamagnetic core. Subsequently, USP is employed to thermally decompose gold precursors, generating gold nanoparticles that nucleate and partially coat the Fe_3O_4 surface, while some free AuNPs are also formed. The resulting nanostructures are crystalline and predominantly spherical, with particle sizes ranging from 10 to 200 nm. Although the materials exhibit a plasmonic response from the gold component and retain a superparamagnetic core, the saturation magnetization is reduced to approximately 0.1 emu g^{-1} , and colloidal stability is poor with a zeta potential near 0 mV, leading to visible aggregation. Despite these limitations, the hybrid system shows potential for biomedical imaging, drug delivery, and plasmon-enhanced magnetic diagnostic applications [35].

Table 2 provides a concise summary of the various physical synthesis methods discussed, highlighting the typical morphologies, size ranges, key properties, and major applications of the resulting nanoparticles. The physical sputtering followed by thermal annealing method offers a straightforward and scalable route for fabricating surface-enhanced Raman scattering (SERS)-active substrates. In this approach, a thin gold film is sputtered onto silicon or quartz substrates using a current of 10 to 20 mA for 20 to 40 seconds. The deposited film is subsequently annealed at temperatures between 300 and 500 $^{\circ}\text{C}$ for one hour to induce film agglomeration into nanoscale gold structures. During annealing, surface diffusion and dewetting lead to the formation of irregular gold nanostructures, with particle size, spacing, and surface roughness increasing with the initial film thickness. The resulting morphology, and consequently the SERS performance, is effectively tuned by adjusting the sputtering current, deposition time, and annealing temperature [36]. These substrates exhibit Raman enhancement factors of approximately 100 to 200 times, offering a simple, low-cost, and scalable route for fabricating SERS-active surfaces suitable for biomedical sensing, chemical detection, and industrial trace analysis [6].

A more sophisticated variant, the combinatorial magnetron sputtering followed by annealing approach, employs a gradient strategy to optimize nanoparticle properties. Gold layers with graded thicknesses ranging from 1.6 to 7 nm are deposited onto fused silica substrates and subsequently annealed to induce dewetting and nanoparticle

formation. This gradient strategy generates spatially varying gold nanoparticle sizes and packing densities, with denser nanoparticle assemblies observed at film thicknesses of 2 to 4 nm and an optimal plasmonic response at approximately 7 nm. High-throughput optical scanning combined with finite element method (FEM) modeling is employed to identify regions with maximum near-field enhancement and sensing performance. This method enables precise tuning of SERS activity and gas sensitivity, offering a powerful platform for optimized Raman, molecular, and gas sensing, as well as for database generation and machine-learning-assisted design of sensing materials [6].

Finally, a femtosecond laser-assisted method has been developed to produce stable, size-tunable gold nanoparticles with low dispersity. This method involves the formation of initial nanosized seeds, typically smaller than 10 nm, by laser ablation from a gold target in aqueous solutions of biopolymers. By carefully controlling the laser parameters and the biopolymer concentration, nanoparticle sizes can be tuned across a broad range from approximately 3 to 80 nm, offering a versatile route to high-purity, stabilized nanoparticles suitable for a variety of applications [10].

3.3. Biological Synthesis

Biological synthesis, often termed green synthesis, has emerged as a compelling alternative to conventional chemical and physical methods for producing gold nanoparticles. This approach harnesses the inherent reducing and stabilizing capabilities of biological entities, ranging from plant extracts and microorganisms to algae and their derived biomolecules. The fundamental principle underlying

biological synthesis is the bioreduction of gold ions (Au^{3+} to Au^0) facilitated by secondary metabolites such as flavonoids, terpenoids, phenolic compounds, alkaloids, proteins, and polysaccharides. These biomolecules not only reduce the gold precursor but also simultaneously cap the nascent nanoparticles, imparting colloidal stability and often conferring intrinsic biological activity to the nanoparticle surface. This dual functionality eliminates the need for external toxic reducing agents and synthetic stabilizers, making the process inherently eco-friendly, cost-effective, and biocompatible.

Figure 4 provides a comprehensive schematic overview of the biological synthesis paradigm, illustrating the various biological sources, including bacteria, fungi, algae, and plant extracts, that can serve as reducing and stabilizing agents. The figure also highlights the typical steps involved, from the preparation of the biological extract to the formation of functionalized gold nanoparticles, and their subsequent application in areas such as biosensing and biomedicine [37, 38].

Among the various biological sources, plant-mediated synthesis has garnered significant attention due to its simplicity, scalability, and the rich phytochemical diversity of plant extracts. A notable example is the green synthesis of gold nanoparticles using an aqueous leaf extract of *Ziziphus spina-christi*, a plant known for its medicinal properties. As depicted in Figure 5, the biosynthesis procedure involves the controlled reaction of an aqueous gold chloride ($\text{HAuCl}_4 \cdot 3\text{H}_2\text{O}$) solution with the plant extract under optimized conditions. The extract is rich in bioactive phytochemicals, including alkaloids, phenols, flavonoids, proteins, and vitamins, which collectively act as natural reducing and stabilizing agents.

Table 2. Overview of physical synthesis methods for gold nanoparticles, highlighting typical morphologies, size ranges, key properties, and major applications.

Synthesis Method	Typical Morphology	Size Range (nm)	Key Properties	Major Applications
Pulsed Laser Ablation in Liquid (PLAL)	Spherical	5–50	High purity, ligand-free surface, biocompatible, antibacterial	Antibacterial coatings, photothermal therapy, fundamental studies
Laser Ablation for Core–Shell Structures ($\text{Au}@\text{Fe}_3\text{O}_4$)	Core–shell, spherical	~25	Tunable optical bandgap, high photodetector responsivity	Photodetectors, biosensing
PLAL-Assisted Doping ($\text{CdS}:\text{Au}$)	Thin films with embedded Au	6.6–9.3 (crystallite)	Reduced bandgap, enhanced nonlinear optical properties	Optical modulators, photonic devices
Coprecipitation with Ultrasonic Spray Pyrolysis	Spherical, hybrid ($\text{Au}/\text{Fe}_3\text{O}_4$)	10–200	Plasmonic response, superparamagnetic, poor colloidal stability	Biomedical imaging, drug delivery
Physical Sputtering with Thermal Annealing	Irregular nanostructures	Variable (tunable)	SERS-active, tunable morphology, scalable	SERS-based sensing, chemical detection
Combinatorial Magnetron Sputtering with Annealing	Spatially varied nanoparticle arrays	Variable (1.6–7 nm film thickness)	High-throughput optimization, tunable plasmonic response	Raman sensing, gas sensing, machine-learning-assisted design

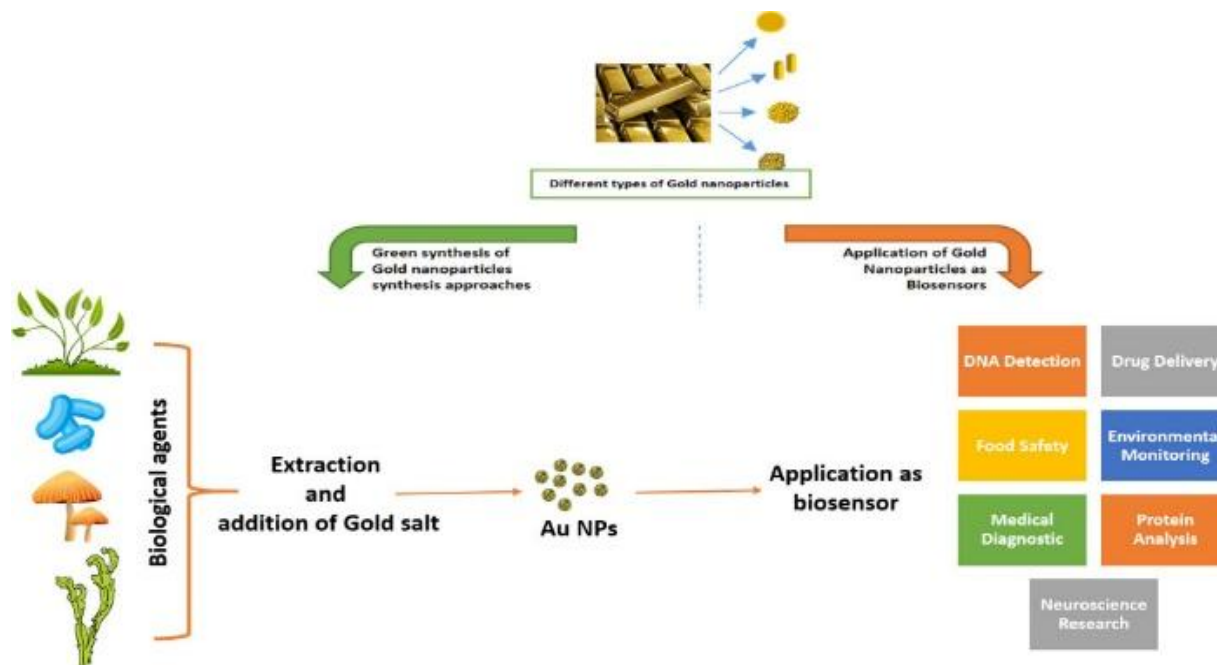


Fig. 4. Schematic representation of the biological synthesis of gold nanoparticles using various biological sources, including plants, bacteria, fungi, and algae. The figure illustrates the key steps from extract preparation to nanoparticle formation and their applications in biosensing and biomedicine. [Reprinted with permission from ref. [37]. Karnwal, A., Sachan, R. S. K., Devgon, I., Devgon, J., Pant, G., Panchpuri, M., & Kumar, G. (2024). Gold Nanoparticles in Nanobiotechnology: From Synthesis to Biosensing Applications. ACS Omega, 9(28), 29966-29982. Licensed under CC-BY-NC-ND 4.0. Copyright © American Chemical Society.]

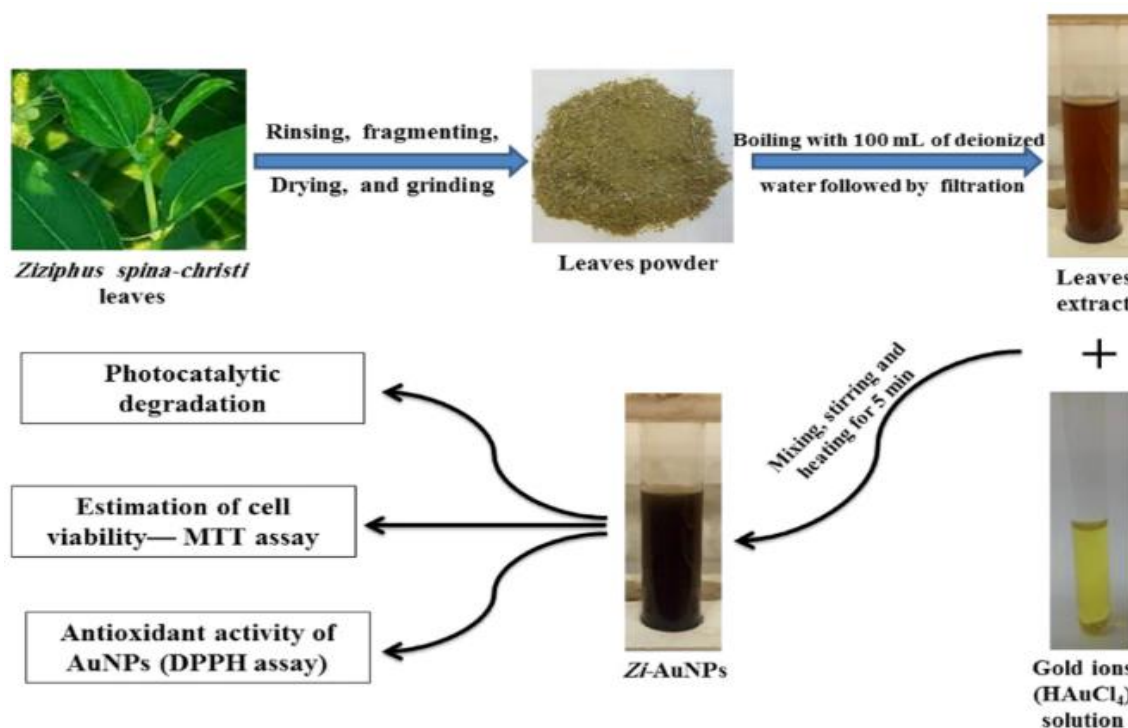


Fig. 5. Schematic illustration of the biosynthesis procedure for *Ziziphus spina-christi*-mediated gold nanoparticles (Zi-AuNPs), showing the stepwise process from leaf extract preparation to nanoparticle formation and characterization. [Reprinted with permission from ref. [39]. Hosny, M., Eltaweil, A. S., Mohamed, M. A. M. T. S. A., El-Badry, Y. A., Hussein, E. E., Omer, A. M., ... & Fawzy, M. (2022). Facile Synthesis of Gold Nanoparticles for Anticancer, Antioxidant Applications, and Photocatalytic Degradation of Toxic Organic Pollutants. ACS Omega, 7(3), 3121-3133. Licensed under CC-BY-NC-ND 4.0. Copyright © American Chemical Society.]

The reaction is typically carried out at 70 °C for 60 minutes under controlled conditions, resulting in the formation of stable gold nanoparticles. Characterization using transmission electron microscopy (TEM), field emission scanning electron microscopy (FE-SEM), atomic force microscopy (AFM), and X-ray diffraction (XRD) confirmed that the synthesized nanoparticles exhibit a predominantly spherical morphology with particle sizes ranging from 31.26 to 58.06 nm. Owing to their biogenic surface functionalization and excellent colloidal stability, these *Z. spina-christi*-mediated AuNPs demonstrated significant potential for biomedical applications. In particular, they showed remarkable efficacy in photothermal therapy for breast cancer treatment, where near-infrared (NIR) irradiation induced localized hyperthermia, leading to apoptosis of cancer cells, thereby highlighting their promise as a therapeutic nanoplatform [38].

Beyond terrestrial plants, marine resources have also proven to be excellent biofactories for nanoparticle synthesis [39-46]. Gold nanoparticles were successfully synthesized using an aqueous extract of dried whole *Halymenia pseudofloresii*, a red alga. The seaweed extract is rich in phenolic compounds and carboxyl functional groups, which serve simultaneously as reducing and capping agents, enabling effective bioreduction of gold chloride under mild reaction conditions. The synthesis was carried out at 60 °C for 20 minutes, resulting in well-stabilized AuNPs with an average particle size of approximately 27 nm and predominantly cubic and rectangular morphologies. Comprehensive characterization using UV-vis spectroscopy, XRD, Fourier-transform infrared (FTIR) spectroscopy, and SEM confirmed the structural, optical, and surface chemical characteristics of the synthesized nanoparticles. The biofunctionalized AuNPs exhibited remarkable biological activities, including strong antioxidant and antibacterial effects, with efficient inhibition of *Staphylococcus aureus*, *Lactobacillus*, and *Pseudomonas aeruginosa*. Furthermore, the nanoparticles demonstrated potent anticancer activity against A549 human lung cancer cells, with a remarkably low half-maximal inhibitory concentration (IC₅₀) value of 19.02 µg mL⁻¹, underscoring their potential for biomedical and therapeutic applications [6].

Ultrasonic-assisted green synthesis has emerged as an effective strategy to enhance reaction kinetics and control nanoparticle size distribution. Gold nanoparticles were synthesized using an extract of the aerial parts of *Satureja khuzestanica*, a plant endemic to the Middle East. The plant extract, enriched with phenolic compounds, flavonoids, and terpenoids, functioned effectively as both reducing and capping agents during the bioreduction of gold chloride [22, 40]. The synthesis involved mixing the plant extract with the gold salt solution, followed by ultrasonic treatment at 60 °C for 40 minutes to promote nucleation and controlled growth, and subsequent rotary evaporation to obtain stable nanoparticles. The resulting AuNPs exhibited a uniform cubic morphology with particle sizes in the range of 20 to 30 nm. Comprehensive characterization using UV-vis spectroscopy, SEM, XRD, and FTIR confirmed the

formation, crystallinity, surface functionalization, and morphology of the nanoparticles. Biologically, the *S. khuzestanica*-mediated AuNPs demonstrated significant antiparasitic activity against hydatid cyst protoscoleces, inducing apoptosis via caspase-3 activation and causing pronounced ultrastructural cellular damage. Importantly, they exhibited low cytotoxicity toward normal human cells, highlighting their strong potential for safe biomedical and antiparasitic applications [41-46].

Figure 6 presents high-resolution transmission electron microscopic images and corresponding surface plasmon extinction spectra for gold nanoparticles of different morphologies, both before and after surface modification with polyethylene glycol (PEG). The top panel shows CTAB-covered spherical, urchin, and rod-shaped nanoparticles, while the bottom panel displays the same particles after PEGylation. The corresponding spectra in panels (a) through (f) illustrate how the surface plasmon resonance shifts as a function of both morphology and surface chemistry. This figure underscores the critical importance of characterizing not only the core nanoparticle morphology but also the surface coating, as both factors profoundly influence the optical properties and biological interactions of the nanoparticles [47].

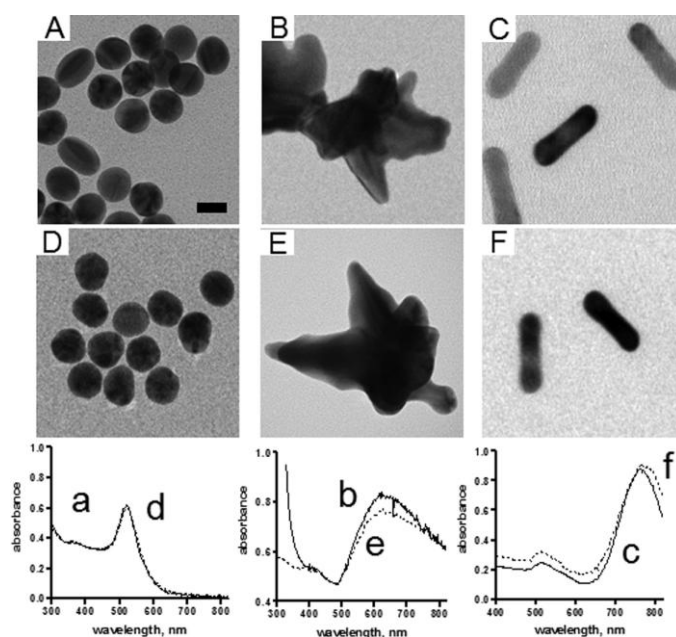


Fig. 6. Transmission electron microscopic images and surface plasmon extinction spectra of gold nanoparticles. Top panel: CTAB-covered spherical (A), urchin (B), and rod (C) GNPs. Bottom panel: PEGylated spherical (D), urchin (E), and rod (F) GNPs. Scale bar is representative for all panels (20 nm). (a-f) Corresponding spectra. Solid line, CTAB-covered GNPs; dashed line, PEGylated particles. [Reprinted with permission from ref. [47]. Hutter, E., Boridy, S., Labrecque, S., Lalancette-Hébert, M., Križ, J., Winnik, F. M., ... & Maysinger, D. (2010). Microglial Response to Gold Nanoparticles. *ACS Nano*, 4(5), 2595-2606. Copyright © American Chemical Society.]

Table 2 provides a comprehensive overview of the commonly used synthesis methods for gold nanoparticles, encompassing chemical, physical, and biological approaches. For each method, the table summarizes the typical morphologies obtained, the size range, key physicochemical properties, major applications, and representative references, offering a comparative perspective on the diverse synthetic landscape.

The biological synthesis represents a rapidly advancing frontier in gold nanoparticle fabrication, offering a sustainable, biocompatible, and often functionally enriched alternative to conventional methods. The diverse array of biological sources, from terrestrial plants to marine algae, provides a rich palette for tailoring nanoparticle properties. The intrinsic surface functionalization imparted by biomolecules not only stabilizes the nanoparticles but also often confers additional biological activities, such as antibacterial, antioxidant, or anticancer properties, creating opportunities for the development of integrated therapeutic and diagnostic platforms. As the field progresses, further elucidation of the mechanistic roles of specific phytochemicals, standardization of synthesis protocols, and rigorous assessment of long-term stability and safety will be

essential for translating these green-synthesized nanoparticles from the laboratory to real-world biomedical and environmental applications.

4. CHARACTERIZATION TECHNIQUES

The comprehensive characterization of gold nanoparticles (AuNPs) is essential for establishing reliable structure–property relationships and ensuring the reproducibility of synthesis protocols. Given that the functional performance of AuNPs is dictated by their size, shape, surface chemistry, crystallinity, and colloidal stability, a combination of complementary analytical techniques is routinely employed. Spectroscopic methods provide insights into optical behavior and surface interactions, microscopic techniques offer direct visualization of size and morphology, diffraction methods reveal crystallographic structure, and scattering techniques assess hydrodynamic behavior in suspension. The integrated application of these methods enables a holistic understanding of nanoparticle attributes, which is critical for both fundamental studies and application-oriented development.

Table 2. Overview of commonly used synthesis methods for gold nanoparticles, highlighting their typical morphologies, size ranges, physicochemical properties, and major applications.

Synthesis Method	Typical Structure / Morphology	Size Range (nm)	Key Properties	Major Applications	Ref.
Chemical reduction (Turkevich method – citrate reduction)	Spherical	10–50	Good monodispersity, strong SPR, biocompatible	Biosensing, drug delivery, imaging, catalysis	[42]
Brust–Schiffrin method	Spherical, quasi-spherical	1–5	High stability, thiol-functionalized surface, narrow size distribution	Molecular electronics, catalysis, biomedical labeling	[25]
Seed-mediated growth	Rods, cubes, bipyramids, stars	10–200 (length)	Shape anisotropy, tunable SPR (visible–NIR)	Photothermal therapy, SERS, optical devices	[3]
Electrochemical synthesis	Spherical, irregular	5–20	High purity, controlled growth without reducing agents	Sensors, nanoelectronics	[43]
Green synthesis (plant extracts, microbes)	Spherical, triangular, irregular	5–100	Eco-friendly, low toxicity, biologically active surface	Antibacterial agents, drug delivery, diagnostics	[22]
Physical methods (laser ablation, evaporation–condensation)	Spherical	5–50	High purity, ligand-free surface	Optoelectronics, catalysis, fundamental studies	[33, 35, 44]
Photochemical synthesis	Spherical, plates	5–60	Controlled nucleation via light exposure	Patterning, optical applications	[26]
Microemulsion method	Spherical	2–20	Narrow size distribution, good uniformity	Catalysis, sensing	[9]
Template-assisted synthesis	Nanowires, nanotubes, ordered arrays	20–200	Structural precision, anisotropy	Nanoelectronics, plasmonic devices	[32]

4.1. UV–Visible Spectroscopy

UV–Visible (UV–Vis) spectroscopy is arguably the most rapid and accessible technique for confirming the formation of AuNPs and assessing their optical properties. The technique exploits the phenomenon of localized surface plasmon resonance (LSPR), which arises from the collective oscillation of conduction band electrons upon interaction with incident electromagnetic radiation. For spherical gold nanoparticles, this resonance manifests as a characteristic absorption band typically observed between 510 and 550 nm [45]. The position, intensity, and bandwidth of the SPR peak are exquisitely sensitive to the nanoparticle size, shape, local dielectric environment, and interparticle spacing. A narrow, symmetric peak generally indicates a monodisperse population of well-dispersed nanoparticles, whereas a red shift accompanied by peak broadening often signals an increase in particle size or the onset of aggregation. Conversely, a blue shift may be observed for smaller nanoparticles. Beyond simple confirmation of nanoparticle formation, UV–Vis spectroscopy serves as a powerful tool for monitoring reaction kinetics in real time, assessing colloidal stability over extended periods, and evaluating the success of surface functionalization reactions, as changes in the local refractive index surrounding the nanoparticles produce measurable spectral shifts [21, 48].

Figure 7 illustrates the utility of UV–Vis spectroscopy in characterizing functionalized gold nanoparticles. The figure presents the absorption spectra of as-synthesized polyvinylpyrrolidone (PVP)-coated gold nanoparticles (PVP-GNPs) and PVP-GNPs conjugated with the chemotherapeutic agent doxorubicin (DOX). The characteristic SPR peak, centered on 520 nm for the unmodified PVP-GNPs, is clearly observed. Upon conjugation with DOX, a subtle shift in the peak position and a change in absorbance intensity are evident, demonstrating how UV–Vis spectroscopy can be used to monitor surface modification reactions and assess the integrity of the nanoparticle dispersion following functionalization [49].

4.2. Transmission Electron Microscopy

Transmission electron microscopy (TEM) is widely regarded as the gold standard for direct visualization of nanoparticles at the nanometer to sub-nanometer scale. Unlike spectroscopic techniques that provide ensemble-averaged information, TEM enables the direct measurement of individual nanoparticle dimensions, offering precise data on size, shape, and size distribution [35]. High-resolution TEM (HRTEM) can resolve lattice fringes, providing direct evidence of crystallinity and allowing measurement of lattice parameters, while selected area electron diffraction (SAED) patterns confirm the crystalline phase and orientation of the nanoparticles. This technique is indispensable for correlating synthesis conditions with structural outcomes, such as distinguishing between spherical, rod-like, cubic, or irregular morphologies. However, TEM requires careful sample

preparation to avoid drying artifacts, and statistically significant numbers of particles must be analyzed to obtain reliable size distributions, typically involving the measurement of several hundred to several thousand nanoparticles [6, 30].

Figure 6 shows representative TEM images of gold nanoparticles with different surface coatings and morphologies. The top panel displays CTAB-covered spherical, urchin, and rod-shaped nanoparticles, while the bottom panel shows the same particles after PEGylation. The scale bar of 20 nm provides a clear reference for the nanoscale dimensions. The corresponding extinction spectra in panels (a) through (f) demonstrate how the SPR peak shifts as a function of both morphology and surface chemistry, highlighting the critical interplay between structure and optical properties [47].

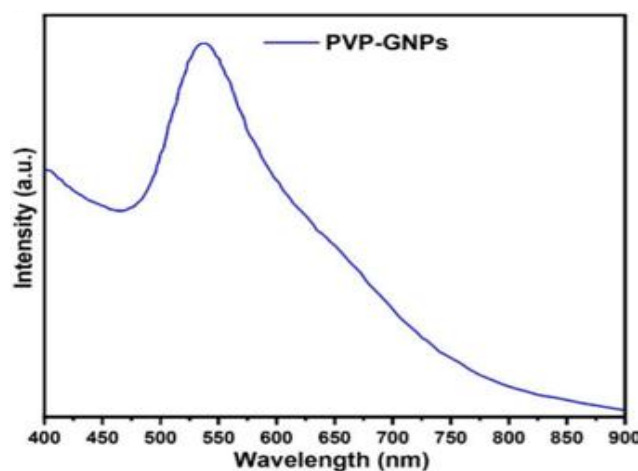


Fig. 7. UV–Vis spectroscopic changes in the spectra of as-synthesized PVP-GNPs and PVP-GNPs conjugated with doxorubicin (DOX). The characteristic surface plasmon resonance peak provides information on nanoparticle formation, dispersion state, and surface modifications. [Reprinted with permission from ref. [49]. Farooq, M.U., Dovzhenko, A.P., Zairov, R.R., Abyzbekova, G., Harb, M., Arkook, B., Akyzbekov, N., Tapalova, A. and Makhlof, M.M., 2024. Insights into the engineered gold nanoparticle-based remedy for supplementation therapy of ovarian carcinoma. *ACS omega*, 9(30), pp.33033–33043. Licensed under CC-BY-NC-ND 4.0. Copyright © American Chemical Society.]

4.3. Dynamic Light Scattering

Dynamic light scattering (DLS) provides complementary information to TEM by measuring the hydrodynamic diameter of nanoparticles in their native colloidal state. The technique analyzes the time-dependent fluctuations in scattered light intensity caused by Brownian motion of the particles. From these fluctuations, the translational diffusion coefficient is derived, and the hydrodynamic diameter is calculated using the Stokes–Einstein equation. Importantly,

DLS measures the size of the nanoparticle core along with any associated surface-bound ligands, polymer coatings, and the surrounding solvation layer, thereby providing a size that reflects the behavior of the nanoparticle in solution. The polydispersity index (PDI) obtained from DLS measurements offers a quantitative assessment of the size distribution breadth, with values below 0.1 indicating monodisperse systems and values above 0.4 suggesting significant polydispersity or aggregation. DLS is particularly valuable for assessing colloidal stability, as it can detect early signs of aggregation that may not be visually apparent. However, the technique has limitations: it is less reliable for polydisperse or highly anisotropic systems, tends to overestimate size compared to TEM due to the inclusion of the solvation layer, and can be influenced by the presence of dust or large aggregates [21].

Figure 8 presents DLS measurements showing the hydrodynamic size and size distribution of gold nanoparticles synthesized with varying molar ratios of trisodium citrate (Na_3Ct) to HAuCl_4 . As the molar ratio increases, a clear decrease in the hydrodynamic diameter is observed, accompanied by a narrower size distribution. The dashed lines represent replicate measurements, demonstrating the reproducibility of the synthesis. This figure illustrates how DLS can be used to systematically optimize synthesis parameters and correlate reaction conditions with the resulting hydrodynamic properties of the nanoparticles [48].

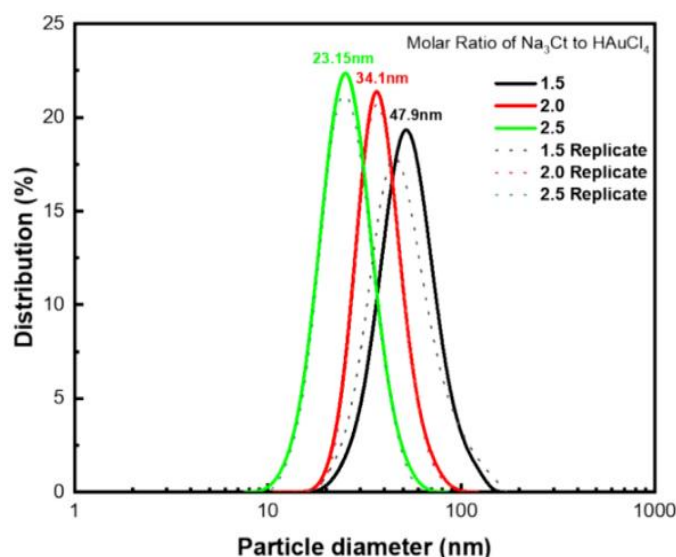


Fig. 8. Dynamic light scattering (DLS) measurements showing the hydrodynamic size and size distribution of gold nanoparticles with varied molar ratios of Na_3Ct to HAuCl_4 (the dashed line represents replicates). The increase in molar ratio resulted in a decrease in hydrodynamic size and narrower size distribution. [Reprinted with permission from ref. [48]. Rivera, R. B. P., Unabia, R. B., Reazo, R. L. D., Lapening, M. A., Lumod, R. M., Ruda, A. G., ... & Alguno, A. C. (2024). Influence of the Gold Nanoparticle Size on the Colorimetric Detection of Histamine. *ACS Omega*, 9(31), 33652-33661. Licensed under CC-BY 4.0. Copyright © American Chemical Society.]

4.4. X-Ray Diffraction

X-ray diffraction (XRD) is an indispensable technique for determining the crystalline structure, phase composition, and average crystallite size of gold nanoparticles. AuNPs crystallize in the face-centered cubic (fcc) structure characteristic of bulk gold, and their XRD patterns typically exhibit distinct diffraction peaks corresponding to the (111), (200), (220), and (311) planes. The presence of these peaks confirms the successful formation of metallic gold and the absence of significant oxide or impurity phases. The broadening of these diffraction peaks is inversely related to the crystallite size, and the Scherrer equation can be applied to estimate the average crystallite dimension. This value often correlates well with the primary particle size observed by TEM, provided the nanoparticles are single-crystalline. Unlike TEM, which provides size information for individual particles, XRD yields a bulk-averaged measurement that is representative of the entire sample, making it particularly valuable for quality control and for confirming crystallinity in samples where direct imaging is challenging [6].

Figure 9 displays the XRD patterns of as-synthesized PVP-GNPs and PVP-GNPs conjugated with doxorubicin (PVP-GNPs-DOX), compared with the standard JCPDS card no. 04-0784 for metallic gold. The characteristic diffraction peaks corresponding to the (111), (200), (220), and (311) planes of the fcc structure are clearly observed, confirming the crystalline nature of the nanoparticles.

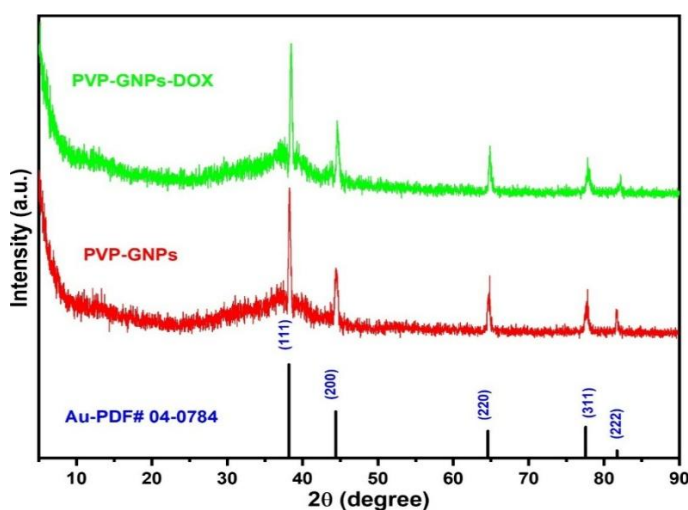


Fig. 9. XRD pattern of as-synthesized PVP-GNPs and PVP-GNPs-DOX, with comparison to standard JCPDS card no. 04-0784. The characteristic peaks corresponding to the face-centered cubic structure of metallic gold confirm the crystalline nature and phase purity of the nanoparticles. [Reprinted with permission from ref. [49]. Farooq, M.U., Dovzhenko, A.P., Zairov, R.R., Abyzbekova, G., Harb, M., Arkook, B., Akyzbekov, N., Tapalova, A. and Makhlof, M.M., 2024. Insights into the engineered gold nanoparticle-based remedy for supplementation therapy of ovarian carcinoma. *ACS omega*, 9(30), pp.33033-33043. Licensed under CC-BY-NC-ND 4.0. Copyright © American Chemical Society.]

The absence of additional peaks indicates phase purity, while the peak broadening is consistent with the nanoscale crystallite size. The figure also demonstrates that the conjugation of DOX does not alter the crystal structure of the gold core, highlighting the robustness of the nanoparticle platform for drug delivery applications [49].

4.5. Complementary Integration of Characterization Techniques

The characterization of gold nanoparticles is most robust when approached as an integrated strategy rather than a collection of isolated measurements. Each technique provides a distinct and complementary perspective: UV–Vis spectroscopy offers rapid, non-destructive assessment of optical properties and dispersion quality; TEM provides direct visualization of size, shape, and morphology with nanometer resolution; DLS evaluates hydrodynamic behavior and colloidal stability in the native solution environment; and XRD confirms crystalline structure and provides bulk-averaged crystallite dimensions. The combined application of these methods enables a comprehensive understanding of nanoparticle attributes, ensuring that the material is well-defined and that its properties can be reliably correlated with synthesis conditions and functional performance. This integrated approach is essential not only for fundamental research but also for the development of reproducible manufacturing protocols and for meeting the rigorous characterization requirements necessary for clinical translation and industrial application of gold nanoparticle-based technologies.

5. CHALLENGES IN AU NANOPARTICLE SYNTHESIS

Despite the remarkable progress achieved in the synthesis of gold nanoparticles (AuNPs) over the past several decades, significant challenges persist that impede their reliable translation from laboratory-scale research to industrial-scale production and clinical application. These challenges span the entire synthetic workflow, from fundamental control over nucleation and growth kinetics to the practical considerations of colloidal stability and batch-to-batch reproducibility. A comprehensive understanding of these hurdles is essential for developing robust synthetic protocols and for realizing the full potential of AuNPs across diverse application domains.

Figure 10 provides a conceptual overview of the multifaceted challenges that accompany the translation of nanotheranostic platforms, including gold nanoparticles, from laboratory discovery to clinical implementation. The figure highlights the interconnected nature of synthesis control, physicochemical property regulation, safety assessment, and regulatory compliance, underscoring that successful translation requires addressing challenges at each stage of the development pipeline [50].

5.1. Control Over Size and Shape

One of the most fundamental challenges in AuNP synthesis lies in achieving precise and reproducible control over nanoparticle size and shape. The formation of nanoparticles is governed by the complex interplay between nucleation and growth kinetics, processes that are exquisitely sensitive to a multitude of reaction parameters. Small variations in precursor concentration, the strength and concentration of the reducing agent, reaction temperature, pH, and mixing conditions can dramatically alter the balance between nucleation events and subsequent growth, often resulting in broad size distributions or the formation of unintended mixed morphologies [51]. This sensitivity is particularly pronounced in the synthesis of anisotropic structures such as nanorods, nanocubes, or nanoprisms, where shape control relies on the selective stabilization of specific crystallographic facets by surfactants or capping agents. The adsorption behavior of these agents is inherently dynamic and can be influenced by subtle changes in reaction conditions, making precise regulation challenging. Furthermore, competing processes such as secondary nucleation, where new particles form after the initial nucleation event, and Ostwald ripening, where larger particles grow at the expense of smaller ones due to differences in surface energy, can further compromise uniformity if reaction conditions are not meticulously controlled throughout the synthesis duration [10]. Achieving monodisperse populations of anisotropically shaped AuNPs therefore demands not only careful selection of reagents but also rigorous control over reaction kinetics and thermodynamics.

5.2. Prevention of Agglomeration

Colloidal stability represents another critical challenge in AuNP synthesis and subsequent handling. Due to their high surface-to-volume ratio, gold nanoparticles possess substantial surface energy and are thermodynamically driven to aggregate, thereby minimizing the overall free energy of the system. Inadequate surface passivation or insufficient stabilization can lead to irreversible agglomeration, which results in the loss of nanoscale properties, including the characteristic surface plasmon resonance, and renders the nanoparticles unsuitable for most applications. To counter this tendency, stabilizing agents such as citrate ions, polymers, or surfactant molecules are routinely employed to provide either electrostatic repulsion, steric hindrance, or a combination of both. However, the concentration and binding strength of these stabilizers must be carefully optimized. Excessive capping can hinder the surface functionality required for subsequent bioconjugation or catalytic activity, whereas insufficient coverage leaves the nanoparticles vulnerable to aggregation.



Fig. 10. Schematic representation of the challenges in translating nanotheranostics from the laboratory to the clinic, including synthesis, precise control of physicochemical properties, safety concerns, and regulatory constraints. [Reprinted with permission from ref. [5]. Kumar, A., Das, N., & Rayavarapu, R. G. (2023). Role of Tunable Gold Nanostructures in Cancer Nanotheranostics: Implications on Synthesis, Toxicity, Clinical Applications and Their Associated Opportunities and Challenges. *Journal of Nanotheranostics*, 4(1), 1-34. Licensed under CC-BY 4.0. Copyright © MDPI.]

Beyond the synthesis itself, environmental factors such as ionic strength, pH, and temperature during storage and application can destabilize colloidal dispersions. For biological applications, exposure to complex media containing high salt concentrations, proteins, and other biomolecules introduces additional challenges, as these components can displace stabilizers or bridge particles, leading to aggregation and altered biological behavior [10].

5.3. Reproducibility and Batch-to-Batch Consistency

Perhaps the most significant barrier to the widespread adoption of AuNP-based technologies is the challenge of achieving consistent reproducibility and batch-to-batch uniformity. While a synthesis protocol may yield well-defined nanoparticles under carefully controlled laboratory conditions, scaling up to larger volumes or transferring the process to different settings often introduces subtle variations that can profoundly affect the final product. Minor differences in reagent purity, mixing efficiency, reaction atmosphere, or heating and cooling rates can produce significant batch-to-batch variability in nanoparticle size, shape, and surface chemistry [50]. This challenge is amplified in green or biological synthesis routes, where the composition of plant extracts or microbial cultures can vary

seasonally, geographically, or with cultivation conditions, introducing an additional layer of uncertainty that is difficult to control. Achieving high reproducibility therefore necessitates rigorous standardization of all synthetic parameters, the implementation of in situ monitoring techniques to track reaction progress in real time, and comprehensive post-synthesis characterization to validate consistency across batches. Such stringent process control is essential for producing AuNPs with reliable and predictable properties, which is a prerequisite for their use in regulatory-sensitive applications such as pharmaceuticals and clinical diagnostics [51-53].

Table 3 summarizes the key challenges in gold nanoparticle synthesis, outlining their underlying causes, potential consequences, and strategies for mitigation. This table provides a concise reference for researchers seeking to understand and address the primary obstacles in the field.

5.4. Integrated Approaches to Overcome Challenges

Addressing these interconnected challenges demands an integrated approach that combines well-defined synthesis strategies with robust stabilization methods and stringent process control. Recent advances in microfluidic reactor technology offer promising avenues for achieving enhanced

reproducibility by providing precise control over mixing, temperature, and reaction time at the microscale, thereby minimizing batch-to-batch variability. Similarly, the application of machine learning and artificial intelligence to synthetic optimization holds potential for navigating the complex parameter space of nanoparticle synthesis, enabling the prediction of optimal conditions for desired outcomes. For biological synthesis routes, efforts to identify and utilize purified active biomolecules rather than crude extracts may help mitigate variability while retaining the benefits of green chemistry. Ultimately, overcoming these challenges is essential not only for advancing fundamental understanding of nanoparticle formation mechanisms but also for enabling the scalable, reproducible, and safe deployment of AuNPs in sensing, catalysis, biomedical, and optoelectronic applications [53]. As the field continues to mature, the development of standardized protocols, robust characterization frameworks, and quality control metrics will be critical for translating the remarkable promise of gold nanoparticles into tangible technological and clinical impact.

6. APPLICATIONS OF AU NANOPARTICLES IN VARIOUS FIELDS

The remarkable physicochemical properties of gold nanoparticles (AuNPs), including their size-dependent optical behavior, high surface reactivity, excellent biocompatibility, and chemical stability, have positioned them as versatile building blocks for a vast array of technological and biomedical applications [54-56]. Their unique characteristics, such as localized surface plasmon resonance (LSPR), ease of surface functionalization, and catalytic activity, enable their deployment across fields

ranging from medicine and catalysis to sensing and optoelectronics. The following sections provide a comprehensive overview of the major application domains where AuNPs are making transformative contributions.

Figure 11 presents a schematic overview of the diverse application areas of gold nanoparticles, illustrating their integration into biomedicine, catalysis, sensing, electronics, and environmental monitoring. This visual summary highlights the multidisciplinary impact of AuNPs and underscores their role as a foundational material across multiple technological sectors.

6.1. Biomedicine and Drug Delivery

Biomedicine represents one of the most extensively explored and clinically promising domains for gold nanoparticle applications. The exceptional biocompatibility of AuNPs, combined with their tunable size and facile surface chemistry, makes them ideal platforms for drug delivery and therapeutic interventions. AuNPs can be functionalized with a variety of targeting ligands, including antibodies, peptides, aptamers, and small molecules, enabling selective accumulation at diseased tissues while minimizing off-target effects. This targeted delivery capability significantly reduces systemic toxicity compared to conventional chemotherapy and enhances the therapeutic index of encapsulated or conjugated drugs [5, 56]. Beyond passive and active targeting, AuNPs serve as carriers for a diverse range of therapeutic payloads, including small-molecule chemotherapeutics, nucleic acids for gene therapy, and proteins for enzyme replacement therapy. The high surface-area-to-volume ratio of AuNPs allows for high loading capacities, while the stability of the gold core ensures protection of labile biomolecules during circulation.

Table 3. Summary of key challenges in gold nanoparticle synthesis, their causes, consequences, and mitigation strategies.

Challenge	Underlying Causes	Consequences	Mitigation Strategies
Size and Shape Control	Complex nucleation and growth kinetics; sensitivity to precursor concentration, reductant strength, temperature, pH, mixing; difficulty in selective facet stabilization	Broad size distributions; mixed or unintended morphologies; loss of property tunability	Rigorous control of reaction parameters; use of seed-mediated methods; in situ monitoring; computational modeling of growth kinetics
Agglomeration Prevention	High surface energy; inadequate surface passivation; insufficient electrostatic or steric stabilization; sensitivity to ionic strength, pH, and storage conditions	Irreversible particle aggregation; loss of SPR properties; reduced functional performance; poor colloidal stability	Optimization of stabilizer concentration and binding strength; use of robust capping agents; surface functionalization; controlled storage conditions
Reproducibility and Batch Consistency	Variability in reagent purity; differences in mixing efficiency and energy input; natural variability in biological extracts; scaling effects	Batch-to-batch variability in size, shape, and surface chemistry; unreliable performance; regulatory barriers to translation	Standardization of protocols; in situ monitoring; comprehensive characterization; statistical quality control; automation and microfluidics

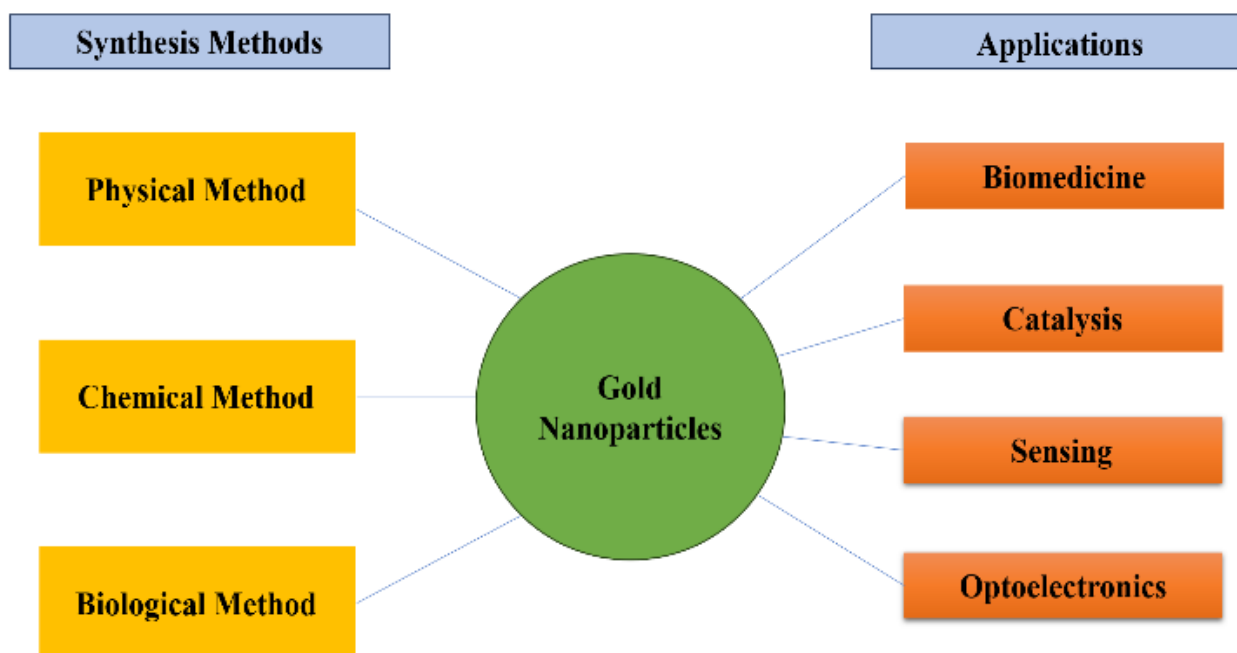


Fig. 11. Schematic representation of the diverse applications of gold nanoparticles across various fields, including biomedicine, catalysis, sensing, electronics, and environmental monitoring.

The photothermal and photodynamic properties of AuNPs have opened new avenues for cancer therapy. Upon irradiation with near-infrared (NIR) light, which penetrates deeply into biological tissues, AuNPs efficiently convert absorbed light into localized heat, inducing hyperthermia and subsequent apoptosis or necrosis of cancer cells. This photothermal therapy (PTT) offers spatial and temporal control over treatment, enabling precise ablation of tumors with minimal damage to surrounding healthy tissue. The efficacy of PTT is particularly pronounced with anisotropic AuNPs such as nanorods and nanostars, whose SPR can be tuned to the NIR window where tissue transparency is optimal [57].

Additionally, AuNPs can serve as photosensitizers in photodynamic therapy (PDT), generating reactive oxygen species upon light activation that induce cell death. In the realm of diagnostics, the strong optical absorption and scattering properties of AuNPs make them invaluable contrast agents for various bioimaging modalities, including computed tomography (CT), two-photon luminescence, optical coherence tomography, and photoacoustic imaging. The high electron density of gold provides excellent X-ray attenuation for CT imaging, while the strong scattering cross-section enables high-contrast optical imaging [57].

6.2. Catalysis

The catalytic properties of gold nanoparticles represent a paradigm shift in the understanding of noble metal catalysis. Bulk gold is widely regarded as chemically inert, but at the nanoscale, gold exhibits remarkable catalytic activity for a

variety of chemical transformations. This size-dependent catalytic behavior arises from the high density of low-coordinated surface atoms, quantum size effects, and the unique electronic structure of nanoscale gold. AuNPs supported on metal oxides such as TiO_2 , CeO_2 , and Fe_2O_3 , or on carbon-based materials, serve as highly effective catalysts for reactions including carbon monoxide oxidation, alcohol oxidation, selective hydrogenation, and the reduction of nitroaromatic compounds [58, 59]. The catalytic efficiency is strongly influenced by nanoparticle size, shape, and the nature of the support material, with smaller particles generally exhibiting higher activity due to their greater proportion of active surface sites [29, 60–62].

In environmental catalysis, AuNPs have demonstrated significant promise for pollutant degradation and green chemical synthesis. Their ability to activate molecular oxygen and facilitate electron transfer processes makes them effective for the oxidative degradation of organic pollutants in wastewater treatment. In electrocatalysis, AuNPs are employed as electrode modifiers for fuel cell applications, particularly in the electro-oxidation of alcohols such as methanol and ethanol, where they exhibit superior activity and resistance to carbon monoxide poisoning compared to platinum-based catalysts [29, 58]. The chemical stability and recyclability of supported AuNP catalysts further enhance their practicality for industrial applications, where long-term durability and cost-effectiveness are paramount.

6.3. Sensing and Biosensing

The exquisite sensitivity of the surface plasmon resonance

(SPR) to changes in the local dielectric environment makes AuNPs exceptionally well-suited for sensing and biosensing applications. The SPR band of AuNPs is highly responsive to alterations in particle size, interparticle distance, and the refractive index of the surrounding medium. These characteristics enable the development of colorimetric sensors, where target analyte binding induces a visible color change detectable by the naked eye or by simple spectrophotometry. AuNP-based sensors have been developed for the detection of a wide range of analytes, including metal ions, small molecules, toxins, DNA sequences, proteins, and pathogenic microorganisms [39, 62]. The versatility of these sensors is greatly enhanced by the ease with which AuNPs can be functionalized with recognition elements such as antibodies, aptamers, and oligonucleotides, enabling highly specific detection in complex biological matrices.

Beyond colorimetric detection, AuNPs serve as superior substrates for surface-enhanced Raman scattering (SERS), a technique capable of single-molecule sensitivity. The intense electromagnetic fields generated at the nanoscale gaps between adjacent AuNPs, often termed "hot spots," provide enormous enhancement of Raman scattering signals, allowing for the identification and quantification of molecular analytes with extraordinary sensitivity [61]. SERS-based detection using AuNP substrates has been applied to disease biomarker detection, pathogen identification, and environmental monitoring. The compatibility of AuNP-based sensing platforms with microfluidic devices and point-of-care diagnostic formats further expands their utility for rapid, low-cost, and decentralized testing [62].

6.4. Optoelectronics

The plasmonic and electronic properties of AuNPs have found increasing application in the field of optoelectronics, where they serve to enhance light-matter interactions at the nanoscale. The ability of AuNPs to confine and concentrate electromagnetic fields into sub-wavelength volumes is exploited in plasmonic waveguides, photodetectors, and light-harvesting devices. In photovoltaic devices, the incorporation of AuNPs into solar cells enhances light absorption through scattering and near-field concentration effects, leading to improved charge carrier generation and, consequently, increased power conversion efficiency [51, 63]. Similarly, in light-emitting diodes (LEDs), AuNPs can enhance light extraction efficiency and modify emission characteristics through plasmonic coupling with excitons in the active layer.

AuNPs are also integral to the development of flexible and printed electronics, where they serve as the active component in conductive inks and pastes. Their nanoscale dimensions enable the fabrication of high-resolution conductive patterns on flexible substrates, facilitating the production of wearable sensors, electronic skins, and rollable displays. In the realm of molecular electronics, AuNPs

function as nanoelectrodes and interconnects, enabling the assembly of single-molecule junctions and the study of charge transport at the molecular scale [54, 64]. The tunable optical response of AuNPs further enables applications in optical switches, metamaterials, and nanophotonic circuits, where precise control over plasmonic resonances is essential for device functionality [63, 64].

Table 4 summarizes the major application areas of gold nanoparticles, highlighting the key properties exploited, representative applications, and relevant references. This table provides a concise overview of the diverse technological domains where AuNPs are making significant contributions. The extraordinary versatility of gold nanoparticles arises from the convergence of their unique optical, catalytic, and surface properties with the ability to precisely control these attributes through synthetic design. From targeted cancer therapy and ultrasensitive diagnostics to efficient catalysis and next-generation optoelectronics, AuNPs continue to drive innovation across an expanding array of technological frontiers. As synthetic methodologies advance and structure-property relationships become increasingly well-understood, the scope and impact of AuNP-based applications are poised for continued growth, promising transformative solutions to challenges in medicine, energy, and environmental sustainability.

7. CONCLUSION

Gold nanoparticles have solidified their status as a quintessential nanomaterial, a distinction earned through a rare convergence of properties: synthetically tunable dimensions, a surface amenable to precise chemical modification, and a plasmonic response that bridges the nanoscale with the macroscopic world. The journey of AuNPs from a colorful curiosity in ancient glassware to a sophisticated platform for modern technology underscores the power of synthetic chemistry to manipulate matter at the atomic level. As this review has detailed, the versatility of AuNPs is intrinsically linked to the chosen synthetic pathway. Classical methods provide a robust foundation for producing spherical nanoparticles, while advanced strategies like seed-mediated growth have unlocked a vast library of anisotropic shapes, each with distinct plasmonic modes that can be tailored for specific functions.

This tunability has been the engine for their widespread adoption across diverse fields. In medicine, they offer a pathway to precision therapies; in catalysis, they challenge long-held assumptions about the reactivity of noble metals; and in electronics, they enable the creation of flexible and printable devices that were once only theoretical. However, translating this laboratory success into widespread real-world application requires addressing persistent challenges. The path forward is contingent on overcoming barriers to large-scale, batch-to-batch reproducibility and developing a deeper understanding of the long-term biological and environmental interactions of these nanoparticles.

Table 4. Overview of major application areas of gold nanoparticles, highlighting exploited properties, representative applications, and key references.

Application Area	Exploited Properties	Representative Applications	Ref.
Biomedicine and Drug Delivery	Biocompatibility, surface functionalization, photothermal effect, strong optical absorption	Targeted drug delivery, photothermal therapy, photodynamic therapy, CT imaging, photoacoustic imaging	[5, 56, 57]
Catalysis	High surface area, size-dependent activity, unique electronic structure	CO oxidation, alcohol oxidation, selective hydrogenation, pollutant degradation, electrocatalysis	[29, 58, 59, 60]
Sensing and Biosensing	Surface plasmon resonance sensitivity, SERS enhancement, ease of functionalization	Colorimetric sensors, SERS-based detection, DNA/protein detection, pathogen identification, point-of-care diagnostics	[39, 61, 62]
Optoelectronics	Plasmonic field enhancement, electronic conductivity, tunable optical response	Solar cells, LEDs, plasmonic waveguides, photodetectors, flexible electronics, molecular electronics	[51, 54, 63, 64]
Environmental Monitoring	Catalytic activity, sensing capability, stability	Pollutant degradation, heavy metal detection, toxin monitoring	[58, 59]
Antimicrobial Applications	Biocompatibility, photothermal effect, surface reactivity	Antibacterial coatings, wound dressings, biofilm disruption	[38, 41]

In conclusion, the story of gold nanoparticles is one of continuous evolution, driven by an ever-deepening understanding of nanoscale physics and chemistry. Their journey from benchtop synthesis to a platform technology exemplifies the translational potential of nanomaterials. Ongoing efforts focused on refining synthetic precision, developing robust and eco-friendly synthesis protocols, and conducting comprehensive safety assessments will be crucial for unlocking the full potential of AuNPs and cementing their role as a foundational material for 21st-century innovation across medicine, energy, and electronics.

8. FUTURE DIRECTIONS

The field of gold nanoparticle research, while mature, stands at an exciting juncture where the focus is shifting from fundamental synthesis to the precise engineering of function and the seamless integration of these nanomaterials into complex, real-world systems. A primary future direction lies in the application of artificial intelligence and machine learning to revolutionize synthetic control. Rather than relying on traditional, time-consuming trial-and-error methods, future research will likely leverage high-throughput synthesis platforms coupled with machine learning algorithms. These models can predict optimal reaction conditions, such as precursor ratios, temperature gradients, and stabilizer concentrations, to achieve a desired size, shape, or surface chemistry with unparalleled accuracy and batch-to-batch reproducibility, a critical requirement for clinical translation and industrial scale-up.

Another pivotal area is the move towards sustainable and intrinsically functional synthesis. While green synthesis using plant extracts has gained traction for its eco-friendliness, it often suffers from batch variability due to the complex composition of biological extracts. Future efforts

will need to focus on identifying and using the purified, active biomolecules responsible for reduction and stabilization. This approach, sometimes termed "bio-inspired" synthesis, could yield a new class of AuNPs with built-in biofunctional surfaces, such as chiral surfaces for enantioselective catalysis or targeted ligands for precision medicine, all without the need for post-synthetic chemical modification.

The application of AuNPs in advanced therapeutics is also poised for significant evolution. The current focus on photothermal therapy will likely expand into more sophisticated, synergistic approaches. One such avenue is the development of "smart" theranostic platforms that combine multiple functions into a single nanoconstruct. For instance, AuNPs could be engineered to carry a chemotherapeutic drug, a gene-silencing RNA molecule, and a molecular imaging agent, all while serving as a photothermal transducer. The future will demand a more rigorous understanding of the nano-bio interface, specifically, the formation of the protein corona and how it dictates cellular uptake, immune response, and eventual biodistribution and clearance. Studies must move beyond simple 2D cell cultures to complex 3D organoid models and, ultimately, to predictive in vivo models that can guide the design of safer and more efficacious nanomedicines.

Finally, a significant horizon is the integration of AuNPs into complex hybrid materials for energy and electronics. While AuNPs have shown promise in flexible electronics and sensors, the challenge lies in creating durable, high-performance devices where the nanoparticles form stable, high-density, and electrically functional networks over large areas. Future work will focus on advanced assembly techniques, such as DNA-directed assembly or interfacial self-assembly, to create ordered nanoparticle superlattices. Such architectures could unlock new collective plasmonic and electronic phenomena, leading to breakthroughs in areas

like high-efficiency photovoltaics, quantum computing components, and ultra-sensitive environmental sensors. The future of gold nanoparticle research is not just about making better nanoparticles, but about designing better systems where these nanoparticles are the fundamental building blocks of a new technological frontier.

DECLARATIONS

Ethical Approval

We affirm that this manuscript is an original work, has not been previously published, and is not currently under consideration for publication in any other journal or conference proceedings. All authors have reviewed and approved the manuscript, and the order of authorship has been mutually agreed upon.

Funding

Not applicable

Availability of data and material

All of the data obtained or analyzed during this study is included in the report that was submitted.

Conflicts of Interest

The authors declare that they have no financial or personal interests that could have influenced the research and findings presented in this paper. The authors alone are responsible for the content and writing of this article.

Authors' contributions

All authors contributed equally to this work.

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