Biointerface Research in Applied Chemistry
Open-Access Journal (ISSN: 2069-5837)

Review
Volume 14, Issue 1, 2024, 12
https://doi.org/10.33263/BRIAC141.012

Synthesis of Gold Nanoparticles and Their Applications in Cancer Therapy

Chitransh Panwar [1], Arushi Phillips [1], Aditi Sangal [1], Deepshikha Gupta [1,*]

[1] Amity Institute of Applied Sciences, Amity University, Sector 125, Noida, India-201301
* Correspondence: dgupta2@amity.edu (D.G.);

Scopus Author ID 56754572800
Received: 29.01.2023; Accepted: 21.02.2023; Published: 2.02.2024

Abstract: Recently, gold nanoparticles (AuNPs) have become important components in biomedical research. They possess various attributes, such as good biocompatibility, inertness, optical properties, and low cytotoxicity, making them applicable in cancer diagnostics and its therapeutic applications. The present paper discusses gold nanoparticles as a drug carrier and the precise delivery of these nano-vehicles to the diseased site. An elaboration has also been done on the basics, historical preview, and different eco-friendly methods used to synthesize gold nanoparticles. Furthermore, we have explained how gold nanoparticle-based delivery vectors have helped in cancer or tumor treatment via photothermal therapy, chemotherapy, photodynamic therapy, and radiotherapy due to their high surface drug loading and controlled drug release at the target site. Finally, despite some limitations of AuNPs, the review helps to effectively understand the importance and achievements of AuNPs as potent tools for next-generation cancer treatment.

Keywords: biocompatibility; cancer; gold nanoparticles (AuNPs); photodynamic therapy; photoimaging; photothermal therapy (PTT).

1. Introduction

Cancer is one of the top causes of mortality around the globe. According to the world health organization (WHO), cancer is a leading cause of death worldwide, accounting for nearly 10 million deaths in 2020, while the number of cancer-related deaths worldwide will exceed 12 million by 2030. As per published data from WHO [1], the common types of cancer prevalent worldwide are depicted in Figure 1. As a result, there is an ongoing need to enhance cancer detection and treatment methods at an early stage. Cancer treatment options now include surgery, chemotherapy, and radiation therapy. As effective as these therapies are, they have several downsides and side effects, such as tissue damage, exhaustion, anemia, related infections, hair loss, long treatment duration, and high cost. To overcome these constraints, it is critical to create innovative anticancer weapons capable of early tumor detection, accurate diagnosis, and customized treatment for various cancer types. Nanomaterials have become a hot topic in cancer therapy in recent years. Because of their tiny size and variable physicochemical qualities, nanoparticles can interact extensively with biomolecules on the surface and within cancer cells. This tremendous engagement capability has the potential to transform cancer care. Because of their great biocompatibility, low toxicity, remarkable penetration into cancer tissues, and, most crucially, nonimmunogenic nature in the human body, gold nanoparticles (AuNPs) stand out as an emerging agent in cancer diagnostics and

therapy. Furthermore, AuNPs have distinct physical and chemical characteristics that provide distinct advantages, including nanoscale, electrical, surface, quantum, and optical impacts [2].

Furthermore, AuNPs are easily produced, with regulated size and shape and a wide range of surface changes. AuNP surface changes have been used to attach targeted ligands, imaging labels, medicinal medicines, and other capabilities [3]. Gold nanoparticles have been used since the 4th century for staining glass as far back as the Roman Lycurgus cup. The glass-staining technique was used since then that contained gold nanoparticles which could both scatter and absorb light, thus looking red or green from different angles [4].

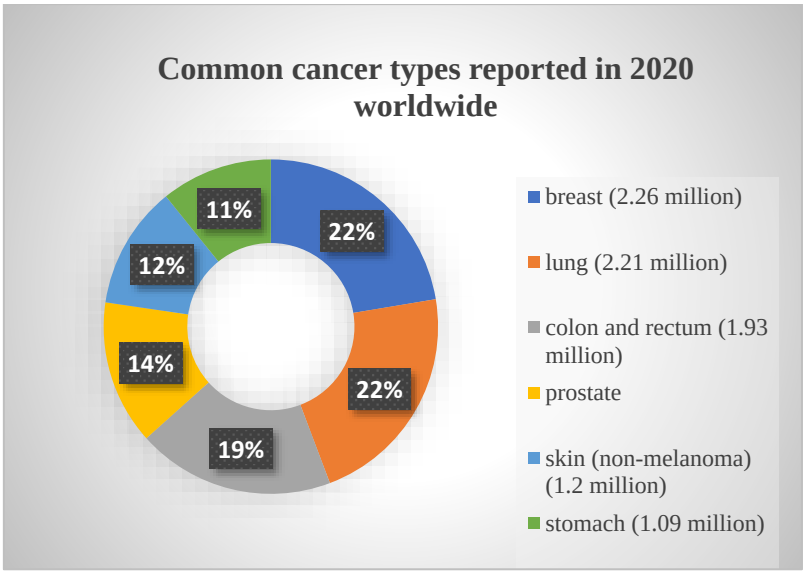

Figure 1. Most common types of cancers reported in 2020 worldwide (in millions).

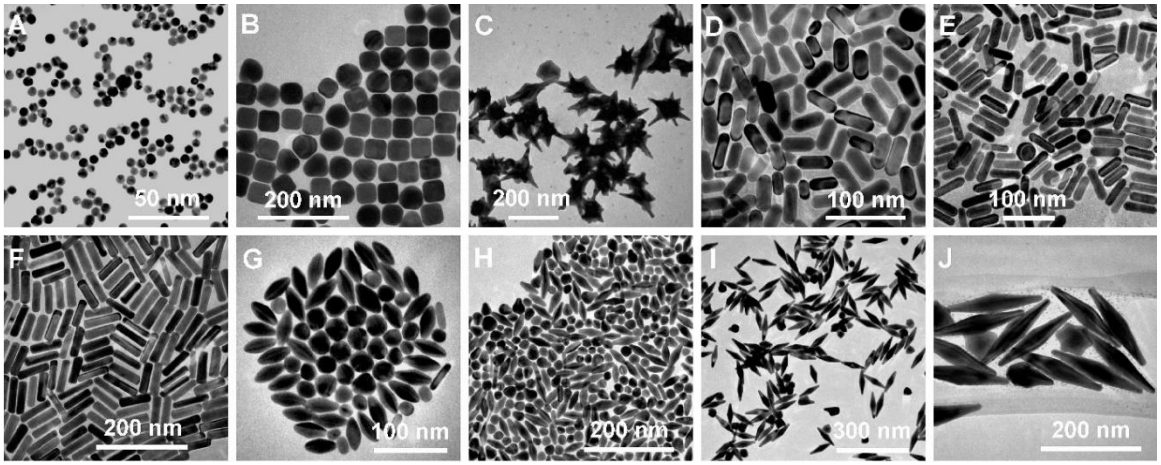

Figure 2. Different TEM images of AuNPs. **(A)** Nanospheres. **(B)** Nanocubes. **(C)** Nanobranches. **(D-F)** Nanorods, **(G–J)** Nanobipyramids. Reprinted with permission from [5] Copyright © 2008, American Chemical Society.

AuNPs have been designed in various forms to address the unique demands of cancer, including Nanospheres, Nanocubes, Nanobranches, Nanorods, and different-sized Nanobipyramids. TEM images of AuNP of different shapes and sizes are represented in Figure 2 as synthesized by Chen *et al*. [5] using tetradecyltrimethylammonium bromide (TTAB), cetyltrimethylammonium bromide (CTAB), ascorbic acid, and sodium citrate dehydrate as stabilizing agents [5,7]. Additionally, AuNPs are naturally nonimmunogenic and have little toxicity. They can easily be regulated in terms of size, shape, and surface alterations. The use of AuNPs for cancer-related applications has thus far been investigated using various cutting-edge strategies, including targeted drug administration, gene delivery, bioimaging, improved

radiation treatment, diagnostics, and light induction therapy [8]. Wider color tenability can be found in plasmonic particles like Au, Ag, and Pt.

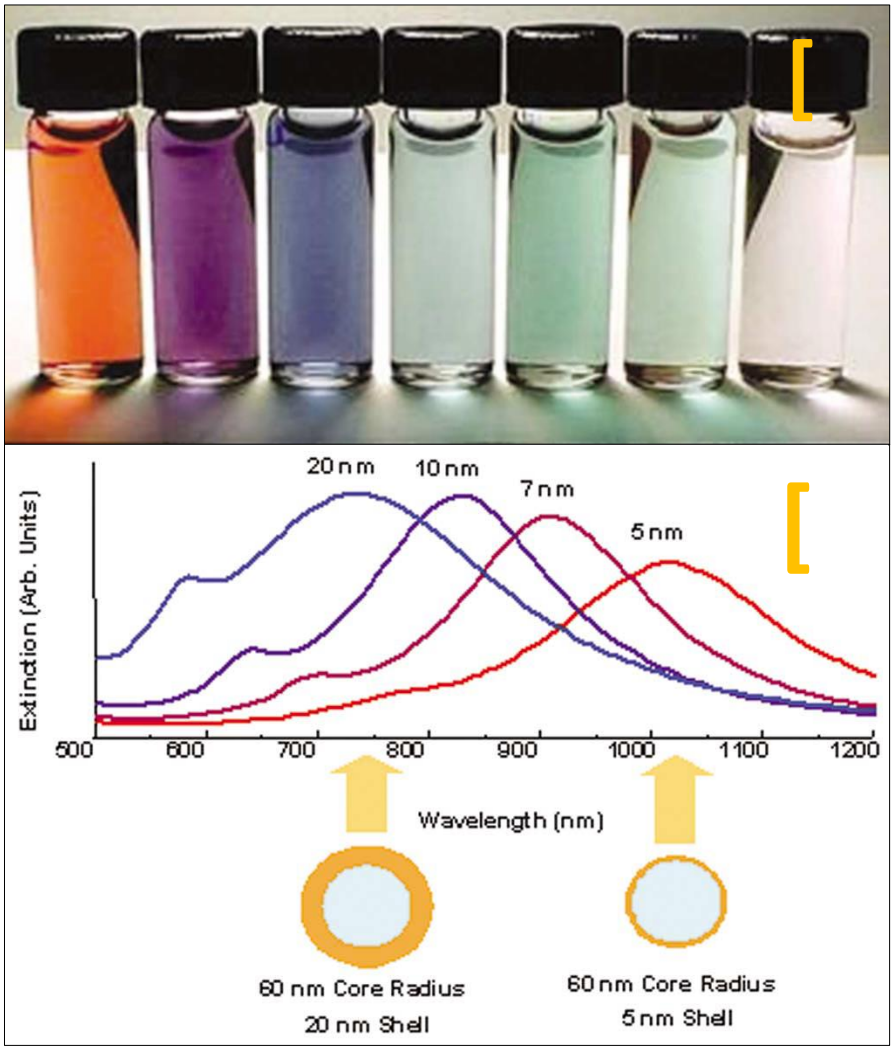

Figure 3. [**A**] Synthetic Tunability of the color of Gold nanoshells exhibiting a broad range of the optical spectrum; [**B**] Optical resonances of gold shell-silica core nanoshells as a function of their core/shell ratio. Reprinted from an open-access article [6].

The color can be changed due to absorption from the ultraviolet through the visible to the near-infrared parts of the electromagnetic spectrum by modifying the nanoparticle size, shape, and composition. The color of silver nanoparticles is a bright yellow, while the color of gold nanoparticles is crimson red. Figure 3 depicts the synthetic tunability of gold nanoshells and absorbance variability of gold shell-silica core nanoshells as a function of their core/shell ratio. The exceptional optical characteristics of AuNPs allow the light to be absorbed and scattered with incredible efficiency. The aggregate oscillation of conduction electrons on metal nanoparticles' surfaces is caused by their interaction with light at a particular wavelength. Because of this oscillation, known as a localized surface plasmon resonance (SPR), the absorbing and scattering intensities of AuNPs are constantly greater than those of comparably sized non-plasmonic nanoparticles. The frequency of the absorption spectrum is intricately linked with the shape and size of the AuNP; this is an essential element since gold nanoparticle absorption may be regulated by tweaking these two deciding variables.

Additionally, the plasmonic nanoparticles can be created to be extraordinarily powerful absorbers, effectively converting light to heat for photothermal therapies and incredibly effective scatters for biodiagnostic properties. Due to all these characteristics, AuNPs may be

functionalized in various ways for the regulated and precise administration of several medications and localized heating of cancerous tissue [9]. AuNP has been studied and used in phase I and phase II clinical studies for cancer therapy because of these remarkable qualities. Size is a crucial factor affecting half-life, systemic toxicity, tumor accumulation, and other crucial characteristics for therapeutic and imaging uses. Understanding the biological effects of AuNPs of various sizes is critical as the number of uses for AuNPs grows. The AuNPs' potential for use in the treatment of cancer essentially rests on their capacity to enter tumor tissues. According to research by Liang and Hong, ultra-small AuNPs in mice demonstrated clear benefits in penetrating tumor tissue [10]. In another recent study reported by Zeeshan *et al*. garcinol bioconjugated AuNPs were found to be more effective inhibitors of glycation reactions than pure garcinol [11].

The following sections will highlight various methods for synthesizing AuNPs; their use as drug carriers has significantly improved cancer detection and therapy. We concentrate on ultrasmall AuNPs, with diameters smaller than 10 nm, in this paper. The techniques for synthesizing and surface functionalizing ultrasmall AuNPs will be covered initially. We shall go into further depth on the uses of ultrasmall AuNPs in cancer therapy, such as radiotherapy, gene therapy, chemotherapy, and other treatments. This information could be important for the ongoing creation of clinical AuNP applications.

2. Synthesis of AuNPs

To date, several methods have been developed to synthesize AuNPs (Figure 4), including chemical, thermal, seeding growth, electrochemical, sonochemical, using ionic liquids, and biological approaches [12].

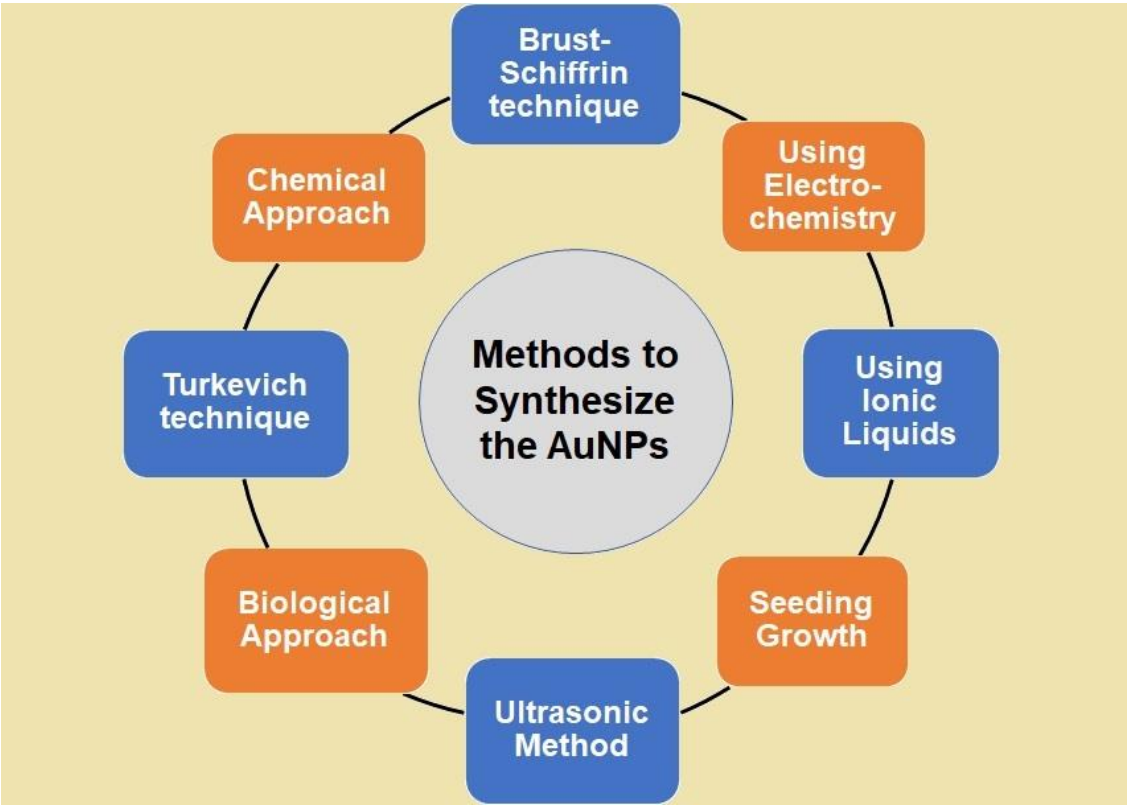

Figure 4. Various approaches used in the synthesis of Nano-gold particles.

It has proven possible to create ultrasmall AuNPs using the wet synthesis technique, which is frequently employed to create bigger AuNPs [13]. Here, we'll pay greater attention to

techniques for efficiently controlling the size of ultrasmall AuNPs. Changing the ratio of reactants is the easiest and most highly used way for producing varying sizes of ultra-small AuNPs. Jaffray *et al*. created various AuNP sizes by altering the proportion of the reducing agent to the gold salt [14]. Liang *et al*. created various AuNP sizes by altering the sodium citrate solution's volume [15].

Additionally, two unique techniques may be applied to control the size of AuNPs. Adding ligands is one technique to regulate the size of the gold core. This technique was initially put out by Schmid *et al*. in 1981 to create Au55(PPh3)12Cl6, which has been extensively studied in models of metal-based catalysis [16]. Based on this, Hutchison *et al*. used a ligand exchange process to modify the gold core's diameter from 1.4 nm to 10 nm [17]. The use of a special carrier as the scattered inner cavity is the second technique for regulating the size of AuNPs. According to Zhang *et al*., a technique for controlling size involves forming carbon nanospheres and AuNPs simultaneously following a reduction procedure [18]. By *in situ* growth in a 2-D mixed ligand metal-organic framework (MOF) nanosheet, Yan *et al*. were able to create very tiny AuNPs (1 nm). Novel 2D nanosheet of mixed-ligand MOF was fabricated, which acted as a good matrix to grow and stabilize the ultrasmall Au-1@NMOF-Ni composite that exhibited prominent catalytic activity, excellent recyclability and intact microporosity of NMOF-Ni [19].

Most of these methods frequently require a hazardous protective agent together with harmful reducing agents such as sodium borohydride, hydrazine, and triethylamine. The outcomes of biological testing, such as toxicity tests in different types of cells, using chemically produced AuNPs were frequently inconsistent [20]. Some research demonstrates a harmful impact, whereas other investigations indicate no detectable cytotoxicity. The fact that the chemicals present in the AuNP solution were not eliminated before this testing significantly contributes to the inconclusive results. If AuNPs are not stable, they may also experience size and shape alterations in biological conditions [21]. For biological applications, it is preferred to use a nontoxic method that produces size- and shape-controllable AuNPs that are stable in biological conditions. One of the most capable techniques is using natural materials such as natural plants' roots, rinds, leaves, petals, and fruits, which include various naturally occurring antioxidants with reducing ability, to convert Au^{3+} to AuNPs [22,23]. Due to its nontoxicity, accessibility, and renewable nature, fruit juice and/or extracts that contain metabolites such as alkaloids, flavonoids, phenols, terpenoids, alcohols, sugars, and proteins have drawn a lot of interest in the green synthesis of AuNPs. They also act as a capping agent and stabilizer for them [24,25]. A very quick rate of synthesis is achieved, and the AuNPs produced appear to be stable. Thus, synthesis employing plant extracts has ushered in a new era in the quick creation of AuNPs due to their nontoxic nature [26]. *Citrus sinensis* extract from biowaste peels was delicately employed as a reducing agent to create uniform-sized AuNPs by managing pH and sodium hydroxide addition sequence. From freshly prepared Citrus sinensis peel extract, stable AuNPs with an ultrasmall size of 2 nm were effectively produced by Yang *et al*. [27]. TEM images of AuNPs formed using *Citrus sinensis* peel extract at pH of 3, 6, 8, 10, and 11 revealed the spherical shape, but sizes decreased with an increase in pH of the solution. Green synthesis of gold nanoparticles (AuNPs) from *Penicillium citrinum*, a marine endophytic fungus, is reported by Manjunath *et al*. [28]. Synthesis of gold nanoparticles (AuNPs) using *Aspergillum* sp. showing excellent catalytic activities for both nitroaromatics reduction and azo dyes decolorization was reported by Qu *et al*. [29]. Lee *et al*. reported the synthesis of AuNPs with a mean diameter of 23 nm from *Inonotus obliquus* (Chaga mushroom) extracts at room

temperature that showed excellent antibacterial, antioxidant, and cytotoxicity against the MCF-1 human breast cancer cell line and NCI-N87 human stomach cancer cell line [30]. Enzymes like α-amylase were used to readily synthesize and stabilize Au NPs in an aqueous solution by Rangnekar *et al*. [31].

In general, there are two basic components to the chemical reduction technique used to generate AuNPs. In the first method, reducing agents like borohydrides, amino boranes, formaldehyde, hydrazine, hydroxylamine, polyols, citric and oxalic acids, sugars, hydrogen peroxide, carbon monoxide, sulfites, hydrogen, acetylene, electron-rich transition-metal sandwich complexes are used; in the second method, compounds like trisodium citrate dihydrate, ligands containing S, P, O, N atoms, dendrimers, polymers, stabilizing agents (CTAB) are used. In order to prevent the particles from aggregating, a stabilizing agent of some sort is typically applied [32].

One of the most well-known methods for creating AuNPs was developed by Turkevich in 1951 and is based on the reduction of $HAuCl_4$ by citrate in water. The trisodium citrate dihydrate is quickly added to the boiling $HAuCl_4$ solution while vigorously stirring. The solution turns from bright yellow to wine red after a short while to produce AuNPs with a 20 nm diameter. Citrate ions perform a dual function in this method, acting as both stabilizing and reducing agents [33,34]. Frens improved the Turkevich process in 1973 so that it could produce AuNPs with diameters ranging from 15 to 150 nm by manipulating the ratio of the stabilizing agent to the reducing agent (trisodium citrate/gold). Numerous research teams have further modified the Turkevich-Frens approach [35]. According to research by Kimling *et al*., a high citrate concentration more quickly stabilizes AuNPs of smaller sizes, but a low citrate concentration causes the small particles to aggregate into larger particles [36]. Herizchi *et al*. has reported the role of sodium citrate on a solution's pH and regulating the size of the using a theoretical model. The presence of nanoparticles was suggested [37,38]. According to Puntes *et al*., adding reagents in the reverse order (adding $HAuCl_4$ to a simmering sodium citrate solution) results in the formation of AuNPs with a limited size range [39]. Numerous studies have examined the effects of temperature, pH, citrate concentration, and gold chloride concentrations on the distinctive features of AuNPs produced by employing citrate as the reductant [40]. Brust and Schiffrin developed a technique in 1994 to create AuNPs with regulated size and low thermally and air-stable dispersion. In this method, AuCl4- was reduced by NaBH4 in the presence of dodecanethiol after being transported from an aqueous solution to a toluene phase using tetraoctylammonium bromide (TOAB) as the phase-transfer agent. When the reducing agent is added, the organic material's color changes. The organic phase turns from orange to deep brown upon the addition of the reducing agent. It demonstrates unequivocally the production of AuNPs [41]. The thiol-mediated capping step prevents aggregation of the reduced gold atoms and produces stable organic monolayers on the AuNPs. The synthesized AuNPs can be further modified by ligand place-exchange reactions with different biomolecules to add a variety of specific functionalities to AuNPs in a process called the Murray method [42]. Figure 5 represents the comparative schematic illustration of (A) the Turkevich method, (B) the Brust-Schiffrin method, and (C) the Murray method.

Table 1. Broad methods for synthesis of AuNPs with reagents needed, conditions, and applications.

Methods	Reagent	Briefing	Application	Reference
Turkevich technique	Trisodium citrate, HAuCl4 solution	By using this technique, AuNPs with a 20 nm diameter are produced. Citrate ions perform a dual	The citrate stabilized AuNPs generated by *in situ* synthesis polydispersed AuNPs. Citrate-stabilized AuNPs were also employed as intermediates in further	[33-40]

Methods	Reagent	Briefing	Application	Reference
		function in this method, acting as both stabilizing and reducing agents.	preparations or functionalization, such as the ligand substitution procedure and seed-growth-mediated synthesis.	
Brust Schiffrin technique	$NaBH_4$ in the presence of dodecanethiol	It demonstrates unequivocally the production of AuNPs.	The potency of the reducing agent employed in the Brust-Schiffrin approach is substantially greater than that of citrate used in the Turkevich method.	[41]
Ionic liquids	Alcohol ionic liquids like quaternary ammonium ionic liquids serve as both a stabilizer and reducing agents.	By simply heating quaternary ammonium ionic liquids (QAILs), stable gold nanoparticles were created.	Anion exchange of the ionic liquid moiety leads to aggregation-induced color changes of the gold nanoparticles in aqueous solutions as an optical sensor for anions.	[43-46]
Solvo-thermal Method	$HAuCl_4$, oleylamine, lipids (MHPC, DGS-NTA(Ni) and DPPEPEG2k	The reduction of Au(III) to Au(0) with considerable monodispersion during the solvothermal synthesis of AuNPs from gold salt precursor leads to a color shift from yellow to red indicating nanosized particle formation. Oleylamine serves as a reduction agent as well as a stabilizer for nanoparticle surfaces.	Prepared gold particles (5-6) were selectively clustered via engineered ferritin nanocages that provide multiple conjugation moieties.	[47]
Sol-Gel Synthesis	$HAuCl_4.3H_2O$, Zirconium n-propoxide, 1-propanol, 2-propanol, acetylacetone, N2	The sol-gel approach has more substantial impacts on NP aggregation; AuNPs are the ideal candidates for sol-gel synthesis due to their susceptibility to clumping (aggregation).	AuNPs are stationary within the gels, which is important in technology applications such as ornamental coatings, catalytic apps, and so on. This technology may also be used to synthesize additional noble metal NPs and their composites from low-cost materials with decreased energy usage.	[48,49]
Seed Mediated Growth	HAuCl4, Glass slides, and ITO substrate, PVP, CTAB	The creation of successfully regulated morphology (size and shape) of AuNPs for diverse purposes favors seed-mediated development. The average diameter of the seed varies between numerical values ranging from a few nm to micron size.	Very beneficial for NPs with defined aspect ratios ranging from 8 to 20 nm, which are required for the tunability of various features (for prospective applications) such as solar cells, strain/stress sensors, drug delivery, bioimaging, and catalytic applications. As previously stated, seed-mediated development is quite useful in terms of managing size, which aids in the tuning of the plasmon resonance frequency of AuNP.	[50-53]
Template Directed Growth	Triamine, $HAuCl_4$, DCM, TOAB (tetraoctylammonium bromide), Dialdehyde, $NaBH_4$	Templates are molecular tools utilized in the synthesis of other molecules. It organizes and provides order to the reactants. Only a small amount (stoichiometric amount) of a template is	Via semiconductor and metal precursors, one may produce relevant NPs in greater yield using template-directed synthesis. Template-directed synthesis may also produce Au nanowires and nano-level electronics. We may obtain a homogeneous and well-ordered AuNP	[54,55]

Methods	Reagent	Briefing	Application	Reference
		required to drive pattern development. Because of its transient contact or bonding with the substrate, the template may be separated from the final result after the growing process.	structure using mesoporous silica film as a template.	
Ultrasonic Assisted Synthesis	$Au(NO_3)_3$, HNO_3, NH_4OH	In the ultrasound-assisted approach, requisite energy is supplied to the reaction medium at room temperature by high-intensity ultrasonic waves that utilize fewer stabilizers, surfactants, and co-surfactants.	AuNPs can have many morphologies, such as nanorings and different assemblages, such as cluster-in-cluster. The reaction conditions and parameters are highly controlled in ultrasonically aided synthesis. The process is both quick and energy-intensive.	[56]
Chemical Vapor Deposition (CVD)	Complex of dimethyl gold (III) with coordinated ligands like β-diketones carboxylates, dithiocarbamates, or quinolone	CVD is a simpler procedure that may be utilized to create thin films or layers of AuNPs at a more controlled scale. The approach makes use of standard gold precursors.	CVD may be used to create AuNPs with sizes ranging from 10 to 100 nm while maintaining perfect control over the reaction conditions. Gold films produced by CVD are preferred for usage in microelectronic devices.	[37,57]
Atomic Layer Deposition (ALD)	Au substrates, H_2O_2, piranha solution, conc. H_2SO_4, ultrapure H_2O, 37% HCl, ethanol, N_2 gas, 11-azido-undecanethiol, 5-hexynoic acid, 99.9% CH_3OH, $CuSO_4$. $5H_2O$, sodium ascorbate, methylene chloride	It is a bottom-up technique, a CVD alternative in which gaseous precursor is driven into the reactor in a pulsation manner at a predetermined time. Plasma ALD is a more adaptable expression of ALD, as plasma forms of reactants have been used.	ALD has an obvious advantage when it comes to vaporizing precursors. This procedure may be used to deposit nanolayers of various materials in a variety of ways. AuNPs can be employed in catalysis and contemporary microelectronics, such as reactors in the micron range.	[58,59]

Reetz *et al*. conducted the first investigation into the electrochemical synthesis of nanoparticles in 1994 [60,61]. Their research demonstrated the electrochemical size-selective nanoscale formation of transition metal particles employing tetra alkyl ammonium salts as metal cluster stabilizers in a nonaqueous medium. The electrochemical synthesis method can be used to create gold nanoparticles on the surface of multi-walled carbon nanotubes with glassy carbon electrodes [62]. The electrochemical process has been shown to be superior to other methods of producing nanoparticles due to its simple equipment, low cost, lower processing temperature, high quality, and ease of yield control [63,64].

Huang *et al* [63] (Figure 6) have suggested the electrochemical production of gold nanoparticles in 0.08 M cetyltrimethylammonium bromide surfactant solution and gold plate and platinum plates to form the anode and the cathode, respectively. The size of the particles was controlled by varying the amount of surfactant, the current density, and the growth temperature.

The seeded growth method is another approach that has been published for the synthesis of gold nanoparticles. Gold nanoparticles with diameters between 5 and 40 nm and restricted size distribution were created using the seeded growth procedure. Every size in the 5 to 40 nm range can be generated because particle size can be regulated by the variable ratio of seed to metal salt [65]. This technique is an easy, rapid, and inexpensive approach; sodium borohydride

($NaBH_4$) was utilized as a reducing agent, and trisodium citrate was used as a source of ^-OH ions in the seeding step. Also, hydroxylamine hydrochloride was used as a slow-reducing agent to enlarge 4 nm seeds to 10 nm AuNPs [66].

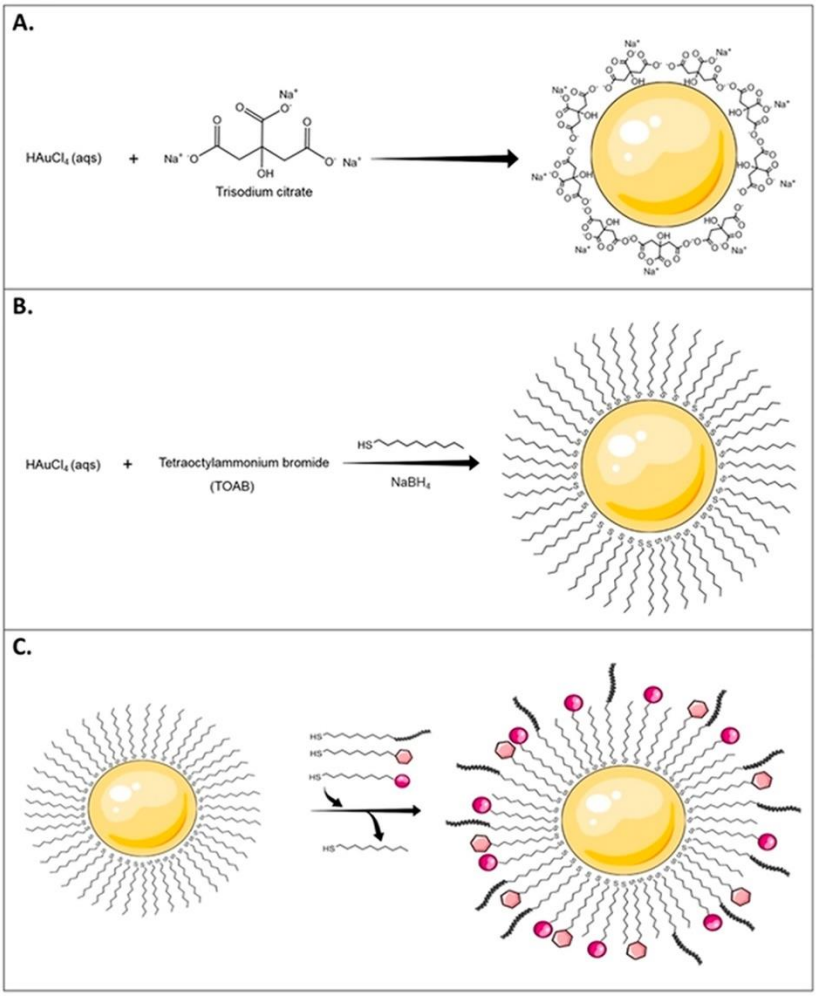

Figure 5. A schematic illustration for Au NPs synthesis by (**A**) the Turkevich method using sodium citrate as a gold-reducing agent and capping agent, (**B**) the Brust-Schiffrin method that includes the use of phase transfer agent (TOAB) and thiol-mediated capping of AuNPs, and (**C**) Murray method or place-exchange method, represented in organo-thiol (-SH) system, which can be used with different ligands and biomolecules. [42] 'International Journal of Nanomedicine 2019 14 7643-7663' Originally published by and used with permission from Dove Medical Press Ltd.

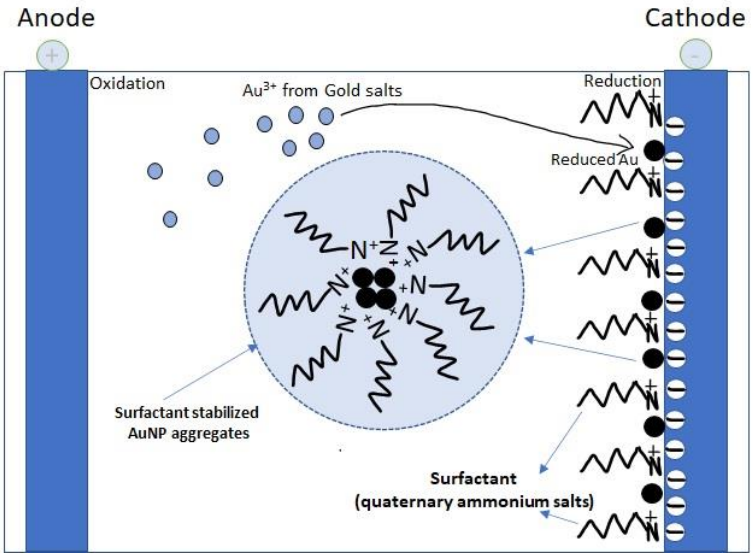

Figure 6. Synthesis of AuNP by an electrochemical method

Although chemical techniques are the most popular way to create metallic nanoparticles, the employment of costly and hazardous chemicals as reducing and stabilizing agents restricts the use of these techniques. Furthermore, the use of these nanoparticles in biomedical applications may also be hazardous. As a result, there is an increasing need to create eco-friendly and economic processes for nanoparticle synthesis without using hazardous chemicals. In recent years, the biological production of nanoparticles has garnered attention as a green and environmentally benign process [67]. Nanoparticles are created biologically by microbes like algae [68], enzymes [69], and plants or plant extracts [23,70,71]. Plant extracts are increasingly being used in nanoparticle production as they are readily available, inexpensive, environmentally friendly, and nontoxic. There have been reports of the biosynthesis of AuNPs using a variety of plants in recent years, including *Azadirachta indica* [70], *Medicago sativa* [72], *Aloe vera* [71], *Cinnamomum camphora* [73,74], *Allium cepa* [75], *Typha capensis* and *Naringenin* [76], propolis extract [77], *Pistacia vera* hull extract [78], mangrove plant - *Ceriops tagal* [79], arabic gum modified magnetic nanoparticles [80].

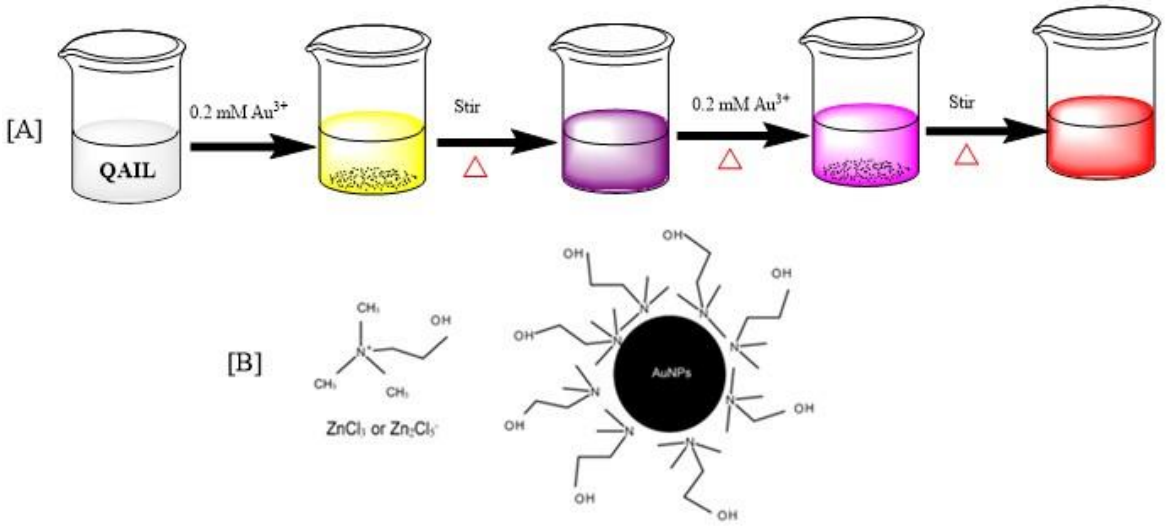

Figure 7. [A] Simple solvothermal method for AuNP formation using QAIL as stabilizing and reducing agents; [**B**] Molecular Structure with stabilized gold nanoparticles.

A one-phase synthesis of AuNPs utilizing thiol-functionalized ILs was described by Kim *et al.* [43]. The stabilizing agents for producing gold nanoparticles were thiol-functionalized ILs. They claimed that the quantity and placement of thiol groups in the ILs had an impact on the size and stability of the nanoparticles. The production of AuNPs in one pot using N-(2-hydroxyethyl)-N-methyl morpholinium tetrafluoroborate was described. Alcohol ionic liquids serve as both a stabilizer and a reducing agent, greatly simplifying the process of making nanoparticles [44]. Figure 7 depicts the molecular architectures of QAILs stabilized gold nanoparticles created by Huang *et al.* [81]. Stable gold nanoparticles were produced by quaternary ammonium-based room-temperature ionic liquids (QAILs), $[Me_3NC_2H_4OH]^+[Zn_nCl_{2n}+1]^-$ (n = 1 or 2), by heating in air at 135–145 °C. The size of the QAIL–AuNPs can be varied between 20 and 40 nm by changing the reaction temperature. Because of the reactivity of their hydroxyl groups, QAILs can be utilized as a solvent, stabilizing agent, and reducing agent. This is because they have good chelating properties. Based on the imidazolium cation, Itoh *et al*. have demonstrated the production of AuNPs modified with ILs. They discovered how to use the anion exchange ability of the imidazolium

cation-based ionic liquid moiety to use the aggregation-induced color changes of the gold nanoparticles in aqueous solutions as an optical sensor for anions [45].

A special way of creating metal nanoparticles is the sonochemical process. The capacity to create extremely small metal nanoparticles and a quick reaction rate are advantages of utilizing this approach to produce metal nanoparticles [46]. However, sonochemically reduced metal nanoparticles typically have broad size distributions. Surfactants and alcohol can help to resolve these issues. However, the size distribution of metal nanoparticles produced by sonochemical reduction is typically very broad. Surfactants and alcohols are frequently utilized in the sonochemical approach to adjust particle size and shape in order to overcome these challenges [82-86]. According to Okitsu *et al.*, Yeung *et al.*, Nagata *et al.*, and Caruso *et al.* [84-87], the sonochemical reduction of Au^{3+} occurs in the following steps: shown in Figure 8. There is a strong influence of increasing ultrasound irradiation on particle size, polyhedral structure, optical properties, and reaction kinetics for their formation. The particle size distribution of the 60 W ultrasonic power sample was 16 ± 3 nm with a faceted pentakis dodecahedron. The self-assembly of molecular polyhedra into complex structures can modify the Au0 atoms with polyhedral shapes in a face-centered cubic (FCC) [88].

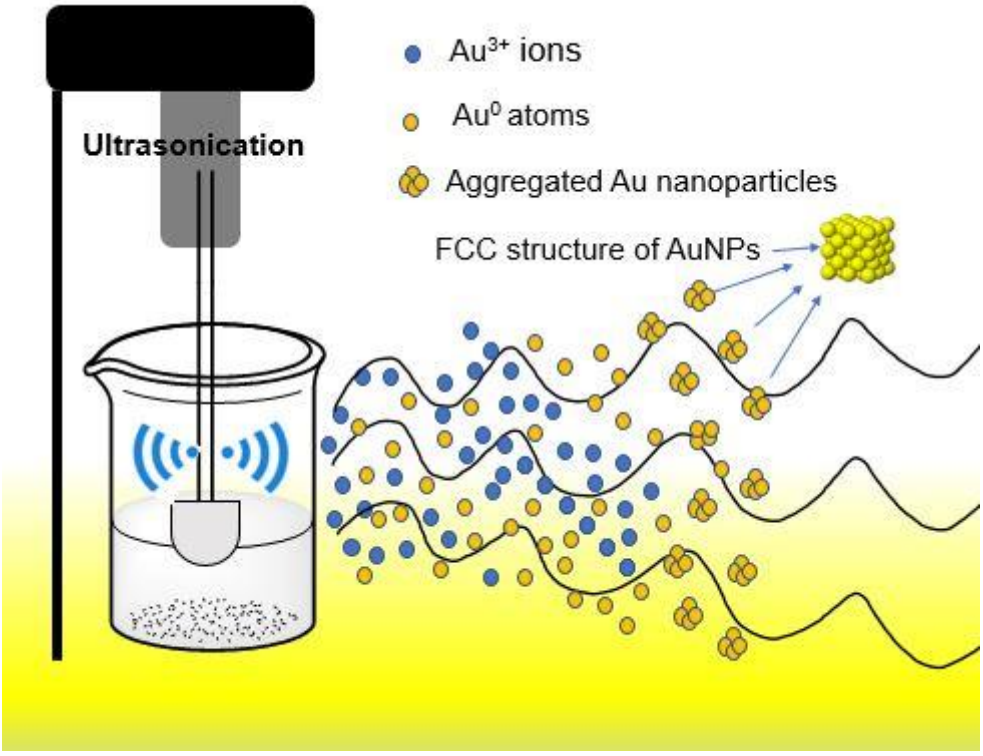

Figure 8. Processing of AuNPs shows nucleation and growth promoted by the sonochemical effect in ultrasonic irradiation in an aqueous solution.

Caruso *et al.* [87] suggested the reduction of $AuCl_4^-$ to colloidal gold in the presence of aliphatic alcohols and sodium dodecyl sulfate in aqueous solutions using 20 kHz ultrasound. Mesoporous silica with gold nanoparticles inside its pores was prepared by the soaking and ultrasound-induced reduction method by Chen *et al.* [89]. Kenji Okitsu and colleagues [84] proposed a sonochemical approach to produce gold nanoparticles (with 22 nm diameter) placed on chitosan powder. A convenient sonochemical method in preparation of gold nanoparticles with a size of 2.7 ± 0.3 nm with narrow uniform distributions and capped by thiol-functionalized ionic liquid (TFIL) using hydrogen peroxide as a reducing agent was described by Jin *et al.* [90] in which function of thiol-containing ionic liquids was to form the bond of S–Au for stabilization of the gold cluster. Gold nanoparticles are synthesized by laser ablation of

a gold plate in toluene [91]. Li *et al.* [92] have suggested microwave-assisted synthesis of magnetic ionic liquid/gold nanoparticles (MIL-Au NPs) as the Surface Enhanced Raman spectroscopy (SERS) substrates for sensitive and reliable determination of clopidol (an anticoccidial agent) residue in egg samples. MIL(1-methyl-3-hexyl imidazole ferric tetrachloride ([C_6mim]$FeCl_4$)) and microwave played a key role in the dispersion and morphology of AuNPs.

3. Biocompatibility of Gold-Nanoparticles

Nanomaterials used in injections and organ grafts must be biocompatible and bioinert. Because these nanoparticles interact differently with mammalian tissues and cells versus their bulk equivalents, their potential cytotoxicity is still being debated. Metal poisoning in the organism is primarily produced by metal cations, which damage cell membranes. On the other hand, gold is very stable in the body and far less prone to ionization than other metals due to its high reduction potential. The previous study has demonstrated that 'Au' is largely safe *in vitro* and *in vivo*, although the diameter and number of 'Au' nanoparticles are recommended to be kept below the limits [93]. The size and form of nanoparticles are important determinants influencing biocompatibility; they are drastically altered by gene regulation, protein absorption, endocytosis, and physical damage to membrane integrity [94]. Vácha *et al*. revealed that the size and form of the gold nanoparticles affected passive endocytosis. Different membrane-binding strengths were discovered, and it was revealed that spherical-shaped gold nanoparticles endocytosed more efficiently than sphere-shaped gold nanoparticles; the transfer of gold nanoparticles with sharp edges was reduced [95].

AuNPs do not cause acute or chronic toxicity. Hence, they are regarded as biocompatible substances. All cancer-related uses of AuNPs rely heavily upon their ability to infiltrate cancer tissues, which varies based on the size, shape, and activity of nanoparticles [96]. These variables are linked with NPs' cellular internalization, half-life, biodistribution, and renal secretion. In this regard, ultra-small AuNPs (diameter approximately 10 nm) have recently demonstrated great performance in decreased toxicity, quicker body clearance, maximal aggregation, and tumor site penetration [97]. Gold nanoparticles as tiny as 2-6 nm can easily cross the blood-brain barrier and reach the tumor nucleus. Furthermore, such ultra-small gold nanoparticles are efficiently removed from the body via the liver, kidney, and glomerulus [98]. Bailly *et al*., for example, demonstrated the safety, pharmacokinetics, and biodistribution of dextran-coated AuNPs in a mouse model and discovered that gold nanoparticles mostly collected in the liver and spleen. There was no hepatic or renal damage [99].

4. Gold NPs as Drug Carriers

Standard chemotherapeutic drug delivery methods, such as intravenous and oral injection, result in drug dispersion throughout the body, resulting in only a portion of the treatment reaching the tumor site. Nevertheless, this might harm normal tissues and organs. This problem is overcome by adopting targeted drug delivery techniques. These techniques are defined as procedures in which a specific bioactive chemical or medication is supplied in a controlled manner to a specific area. For various purposes, such as therapy, imaging, sensing, and so forth, nanoparticles can be used to deliver drugs or other molecules to tumor tissues. This method facilitates quick delivery of the pharmaceutical species to the target location, relatively long persistence within the tissues, and with reduced clearance or deactivation, and thus reduced toxicity and doses than with the lone usage of the drug. Chemotherapeutic

medicines can be linked or loaded on nanoparticles and passively or actively administered to the tumor site. Nanoparticles can easily assemble in tumor tissue due to their leak-prone vascular system. The increased permeability and retention effect is known as the EPR effect. Gold nanoparticles can also exploit passive transport to enhance absorption due to the "leaky" walls of blood arteries in tumors, which allow penetration of relatively large (compared to the typical drug) nanoparticles. This method, however, has certain drawbacks, including arbitrary targeting and poor medication dispersion in tumor cells.

Furthermore, the EPR effect does not appear in all cancers. Monoclonal antibodies, aptamers, vitamins, and proteins are some examples of the ligands of tumor-specific biomarkers that are attached to the nanoparticle surface being actively targeted. Following their interaction with their respective receptors on tumor cells, these ligands cause the drug to be endocytosed and liberated. Therefore, compared to passive targeting, active targeting has a higher potential to result in endocytosis [100,101].

Due to their surface plasma resonance (SPR), optical, and tunable characteristics, AuNPs have piqued the interest of scientists for usage as drug carriers. They may be produced in a varied range of core sizes, making dispersion easier to regulate. Gold nanoparticles are easily changeable due to the existence of a negative charge on their surface. This implies that other biomolecules, including medicines, targeting ligands, and genes, may simply be added to them to make them functional. Furthermore, AuNP biocompatibility and nontoxic nature make them a good option for usage as drug carriers [102]. AuNPs have biological and chemical-physical characteristics that make them ideal for tumor targeting and drug administration, notably in terms of reduced cytotoxicity, ease of synthesis and stability, functionalization, and biocompatibility.

Furthermore, they combine their anticancer activity with the medicines they transport, increasing their effects even further. Since gold nanoparticles are seldom hollow and are nonporous, attaching active molecules to their surface is the best way to transport them. This may be done following proper derivatization and functionalization. When thiols or thiol-derived chemicals are present, the functioning is often accomplished by reducing gold salts, causing the surface to adsorb thiols, which causes the surface to automatically generate strong, non-labile, covalent Au-S bonds that are very stable even in the presence of pH fluctuations. This mechanism is particularly important for AuNP toxicity since they can collect in lymph nodes, spleen, and liver if they are not adequately functionalized to facilitate filtration by the reticuloendothelial system [103]. For example, when methotrexate (MTX, used for long-time cancer treatment) was coupled with gold nanoparticles, it showed increased cytotoxicity against a range of tumor cell lines in comparison to only MTX. It was discovered that MTX accumulated more quickly and to a greater extent in tumor cells when it was combined with gold nanoparticles [104]. In a study conducted by Wang *et al.* [105], doxorubicin (DOX) was attached to 30 nm AuNPs through a pH-sensitive linker that allowed pH-sensitive DOX release from AuNPs inside acidic cellular organelles. The rapid increase in intracellular DOX concentration was evidenced by the recovered fluorescence of doxorubicin from quenching due to the nanosurface energy transfer between the doxorubicinyl groups and the gold nanoparticles. This enhances the therapeutic effects in drug-resistant tumor cells, as depicted in figure 9. Doxorubicin has intrinsic fluorescence in free form, which is a valuable tool in research and imaging.

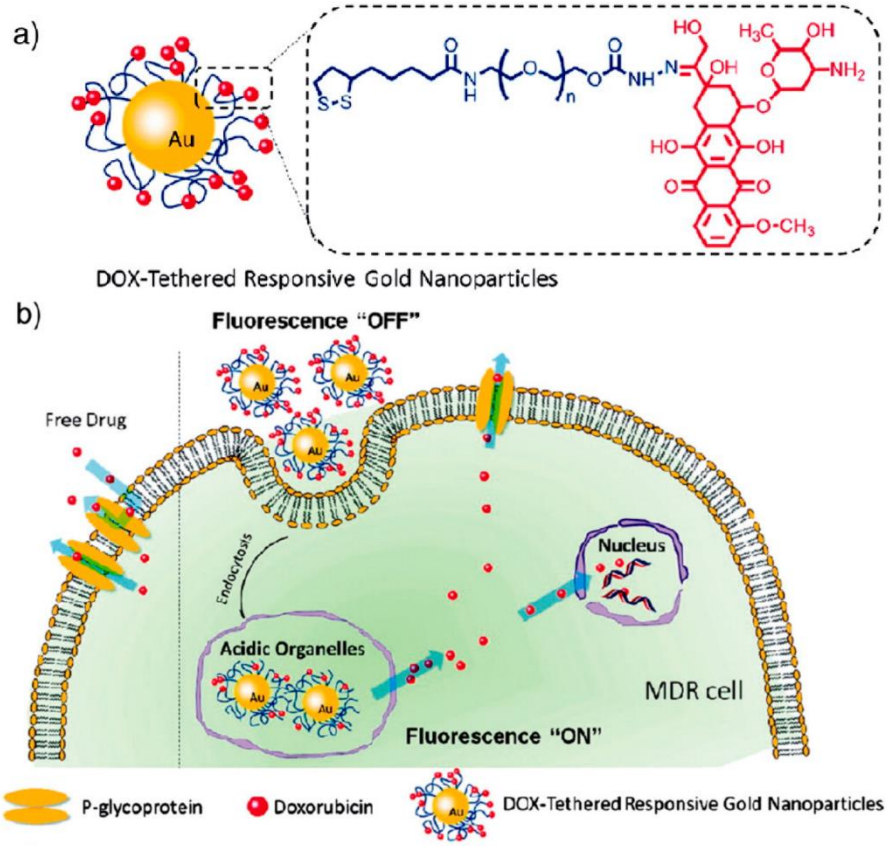

Figure 9. Gold nanoparticle as targeted drug delivery and imaging in cancer cells. Reprinted with permission [105,106] Copyright © 2011 American Chemical Society.

AuNPs have shown significant promise in changing the pharmacokinetic properties of several chemotherapeutic medicines by minimizing nonspecific adverse effects and supplying larger dosages of pharmaceuticals to target areas. This is due to AuNPs' great drug-loading capacity and minimal cytotoxicity. AuNP payloads can range in size from a small pharmaceutical molecule to a large biomolecule like a protein, DNA, and RNA. Medicine loading is determined by characteristics like size, charge, and surface chemical properties [2]. Once within the body, these features influence absorption and eventual intracellular destination. Several cases of chemotherapeutic drugs combined with AuNPs have improved therapeutic advantages in the literature. For example, doxorubicin combined with AuNPs and anti-PD-L1 antibodies has been shown to improve the efficacy of targeted chemo and photothermal therapy in colon-rectal cancer [107]. AuNPs are now in phase I and II clinical trials as cancer therapeutic medications and gene carriers. The NU-0129 medicine, which was created to treat gliosarcoma (brain or spinal cord tumor) based on Spherical Nucleic Acid (SNA) clustered on the surface of AuNPs, is a recent example that can pass the blood-brain barrier (BBB) and block the Bcl2L12 gene, which promotes tumor formation [108]. Overexpression of anti-apoptotic members of the Bcl-2 family, such as Bcl-2 and Bcl-XL, has been implicated in cancer chemoresistance. As a result, the investigations indicated that AuNPs with big and complex shapes have high anticancer potential but lower cellular absorption, and vice versa.

Tiny particles (sub 10 nm) may be excreted from the body more quickly through renal filtration than bigger particles (50–100 nm). Even these smaller nanoparticles can infiltrate tumor tissues deeper and more successfully than their larger counterparts [109]. Scientists have implemented a technique known as 'PEGylation' to protect nanoparticles from immune detection. In this process, nanoparticles "hide" with a polyethylene glycol (PEG) coating. This

masks them from immune detection and prolongs their blood circulation [110]. PEGylation is accomplished by covalent bonding, which captures or adsorbs PEG chains onto the nanoparticle's surface. Polyethylene glycol (PEG) is hypothesized to have a stealth effect that can lengthen the blood half-lives of nano drugs and nanocarriers by lowering nonspecific protein adsorption to some extent [111]. Meanwhile, the EPR effect of PEG makes it particularly beneficial for hiding larger nanoparticles from the intravascular immune system and aiding in targeting cancer cells [112]. However, some research has investigated the influence of PEGylation of ultra-small nanoparticles on blood circulation duration and tissue accumulation quantity, which is one of the utmost essential concerns when considering their biological application, particularly in cancer therapy [113]. PEGylated nanoparticles can be employed for tumor imaging, photothermal therapy, and photodynamic therapy when they get internalized, as depicted in Figure 10. Although PEGylation can prevent fast identification by the reticuloendothelial system (RES), it is seldom possible to achieve total avoidance since the RES system may still detect them. Cytokine (TNF-α) was proven to be a good therapeutic anticancer therapy for its harmful effects on cancerous cells. Later, the TNF- α conjugated PEG gold nanoparticles were used to develop a nanoparticle drug delivery system that effectively enhanced the tumor cell damage. The use of temperature and TNF- conjugated PEG-coated AuNPs led to better therapeutic results than TNF- alone[114].

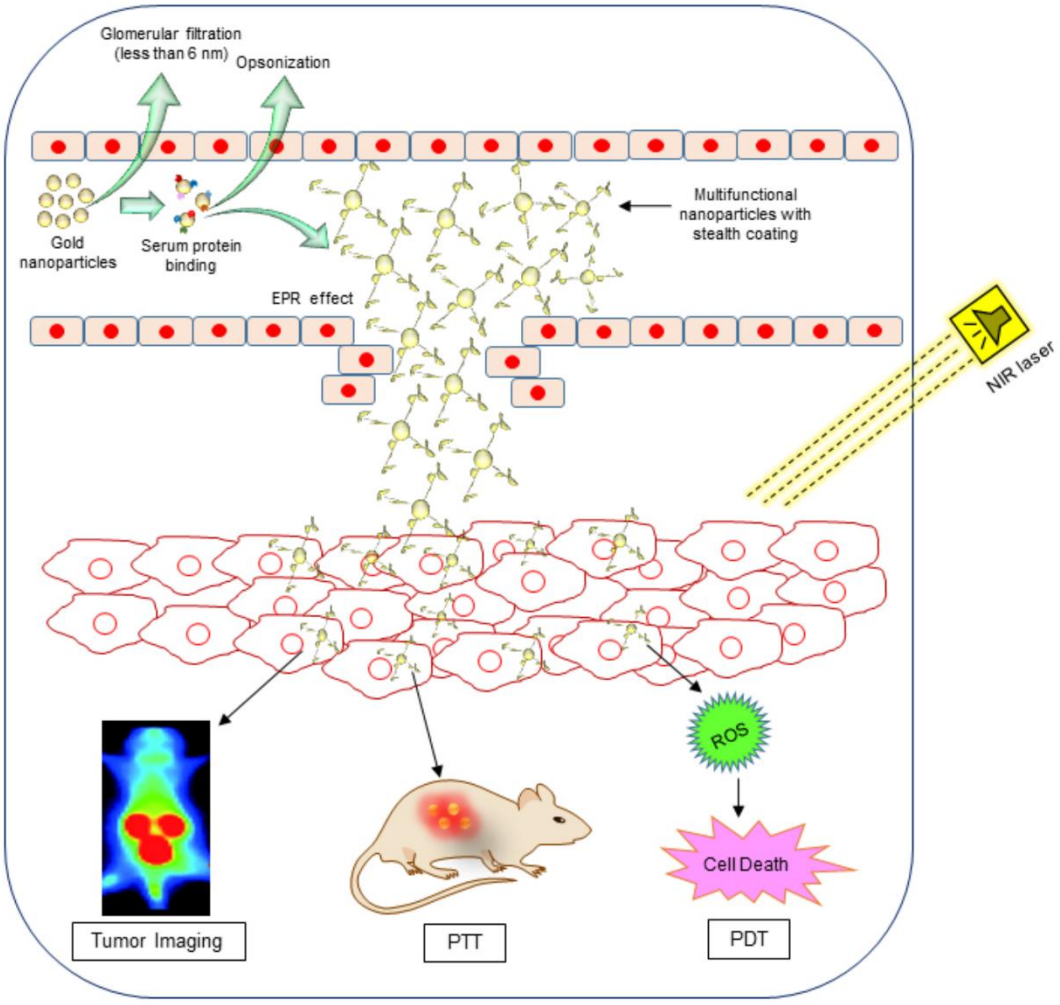

Figure 10. Systemic delivery of multifunctional gold nanoparticles for cancer bioimaging, photothermal therapy (PPT), and photodynamic therapy (PDT). EPR = enhanced permeation and retention; NIR = near infra-red; ROS = reactive oxygen species. Reprinted from an open-access article [114].

The utilization of gold nanoparticles functionalized with fluorescently tagged heparin for the targeted detection and apoptotic death of metastatic cancer cells was reported by Lee *et al.* [115]. The study's central idea was that metastatic cancer cells overexpress heparin-degrading enzymes. Heparin fluorescence was reduced when linked to gold nanoparticles, but it was restored after cleavage by heparinase, allowing cancer cells to be identified. Heparin also binds to arginyl glycyl aspartic acid, an RGD peptide responsible for cell adhesion to the extracellular matrix (ECM), which is overexpressed in cancer cells and induces apoptosis. As a result, these AuNPs might be beneficial for both cancer detection and therapy. Spherical gold nanospheres have been created with photothermal ablation of cancer cells and doxorubicin release when irradiated with NIR light. Drug delivery in tumor cells has been achieved using cylindrical gold nanoparticles containing fluorescein or doxorubicin [116]. In the human glioma cell line LN-229, porphyrin-capped gold nanoparticles were utilized as anticancer drug carriers. When this medication was conjugated into gold nanoparticles, its cytotoxicity was significantly greater than when it was used alone [117].

4.1. Photothermal treatment (PTT).

For their clinical uses, the existence of surface plasmon resonance is important since high light absorption makes the nanoparticles suitable for the treatment of therapeutical substances in so-called photothermal and photodynamic therapies [118]. Photothermal treatment (PTT) is defined as the production of a localized therapeutic temperature by photons, which can trigger hyperthermic physiological reactions. In simple words, when AuNPs are bombarded with the light of the same wavelength as their plasmonic surface absorption spectrum, surface electrons are excited and resonate vigorously, swiftly converting light to heat. Photothermal treatment involves heating cancer cells to 41-47°C for a few minutes and then destroying them by induced hyperthermia. Because human tissues in this range are relatively transparent to near infra- red (NIR) light, this approach using AuNPs has numerous advantages. Their resonance wavelength allows for strong absorption in the NIR area, allowing near-infrared light to penetrate deeper into cancer tissues for more effective therapy. AuNP-based photothermal treatment can be coupled with targeted medication administration or improved tumor identification to boost effectiveness [119]. In a recent review by Nejabat *et al.* [120], gold nanorods showing maximum absorption of longitudinal localized surface plasmon resonance (LSPR) in the near-infrared (NIR) region which overlaps with NIR bio-tissue 'window' suggesting that they are proper tools for thermal ablation of cancer cells. Faid *et al.* have reported higher photothermal heating efficiency of AuNPs with the size of 14±4 nm on MCF-7 (breast cancer cell lines) compared to irradiation without AuNP using a 532 nm laser. Laser irradiation for 6 min along with 0.125 mM concentration of AuNPs significantly reduced (34%) the cell viability, also binding Doxcorubin (Dox) to AuNPs through the –NH group also showed increased cytotoxicity [121].

4.2. Chemotherapy.

Chemotherapy is the process of treating cancer with chemical medications. Chemotherapeutic medications, however, always enter normal cells and result in hazardous side effects. Furthermore, drug efflux pump overexpression, increased drug metabolism, and altered drug targets can all lead to cancer cells developing treatment resistance. Therefore, one of the key challenges of chemotherapy is to boost the concentration of therapeutic medications in tumor cells, hence increasing the treatment's effectiveness and minimizing unpleasant side

effects. It's critical to create effective medication delivery methods in this regard. Given their minimal toxicity and large loading capacity, AuNP-based nanocarriers are considered appealing options for delivering a variety of payloads [96]. In order to deliver a platinum (IV) medication to prostate cancer cells, Kumar *et al*. [122] devised a novel method, as depicted in Figure 11. The anticancer effects of this delivery method on prostate cancer cells were investigated using functionalized Pt(IV) glutathione-modified AuNPs (5.2 nm), Au@GSH, containing the medication and the targeting peptide CRGDK (Cys-Arg-Gly- Asp-Lys) [122]. In this work, the neuropilin-1 (Nrp-1) receptor on the surface of the cancer cells was specifically targeted by the targeting peptide, resulting in improved cellular uptake. This allowed the platinum (IV) medication to target prostate cancer cells only, where its cytotoxic properties killed them off. The nuclear factor kappa-B (NF-B) proteins were elevated in expression, while the functionalized AuNPs triggered NF-DNA-binding B's capability to start platinum-induced apoptosis. These AuNPs showed excellent potential for possible anticancer therapy when functionalized with platinum (IV) and a targeting peptide.

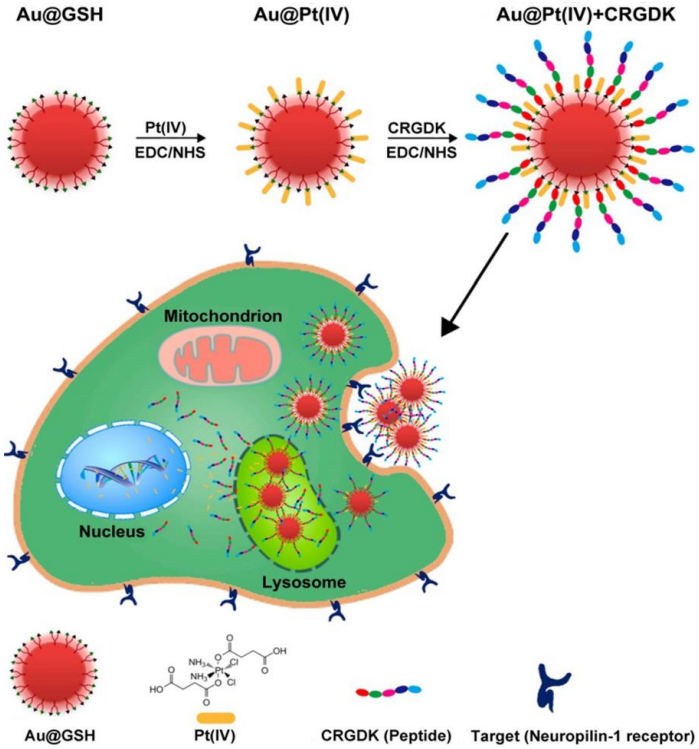

Figure 11. Functionalization of Au@GSH gold NPs with the chemotherapeutic drug Pt(IV) and the targeting peptide CRGDK for cancer treatment. Interaction between the neuropilin-1 receptor and the targeting ligand, which enhances intracellular entry and release of active cisplatin into the nucleus of human prostate cancer cells after endocytosis (receptor-mediated) of the Au@Pt(IV)CRGDK delivery system. Reprinted with permission from [122], Copyright 2014 American Chemical Society.

4.3. Photodynamic therapy.

PDT creates reactive oxygen species (ROS) by energy transfer using oxygen from tissues, light, and photosensitizers (PS), which may be stimulated by light of particular wavelengths. ROS causes cell death through apoptosis. PDT, in contrast to PTT, is wholly dependent on the oxidative properties of ROS [123]. Because of this, the PS's involvement in PDT is crucial; if an appropriate PS is selected, PDT offers the benefits of excellent tolerance, recurrent usage at the same location, and less invasive surgery. PS may be encapsulated or combined with surfaces using AuNPs, which are good biocompatible carriers of PS [124]. It has been observed that AuNPs can boost the singlet oxygen generation (SOG) of different PS

and improve PDT efficiency, and many researchers are striving to produce better PS to increase PDT efficiency [125]. Hone *et al*. made the first demonstration of the production of cytotoxic single oxygen by phthalocyanine stabilized gold nanoparticles [126]. The effectiveness of a Zn(II)-phthalocyanine disulfide (C11Pc)-nanoparticle conjugate as a photodynamic treatment agent in C57 mice with a subcutaneously transplanted amelanotic melanoma was reported by Camerin *et al*. in 2010 [127]. Compared to free C11Pc, the artificial AuNP-bound C11Pc exhibited a more selective reaction to the cancer tissue. The results indicated that the photodynamic treatment induced by C11Pc primarily operated via vascular injury [127]. According to the research that has been published thus far, photothermal and photodynamic treatments are both crucial and successful in the treatment of cancer. As a result, techniques combining these medicines are anticipated to have more effective and potent impacts on cancer cells than PTT or PDT alone. Kuo *et al*. were the first to show in 2010 that AuNPs could be employed jointly as contrast agents in imaging, PTT, and PDT, to image and more effectively destroy malignant A549 cells [128]. The researchers then examined dual-modality PTT and PDT in 2012 utilizing PS that was composed of both AuNPs and gold nanorods coupled with indocyanine green. Comparing the outcomes to PTT and PDT alone, the findings revealed improved photo destruction, photostability, and effective killing of cancer cells [129].

4.4. Radiotherapy.

One of the popular ways to treat cancer is radiotherapy. To eliminate tumor cells, it relies on the application of high-energy radiation. To improve the effectiveness of radiotherapy, radiosensitizers can efficiently increase the radiation dosage at the cellular level. In radiotherapy, AuNPs have the potential to be an outstanding radiosensitizer. This is because AuNPs fasten DNA strand breaks when exposed to gamma or X-rays. Determining which size provides the optimum therapeutic impact is crucial for the efficient use of AuNPs in radiation treatment. Hainfeld *et al*. previously treated animals with X-rays by injecting 1.9 nm-diameter gold particles into mice with subcutaneous EMT-6 mammary carcinomas [130].

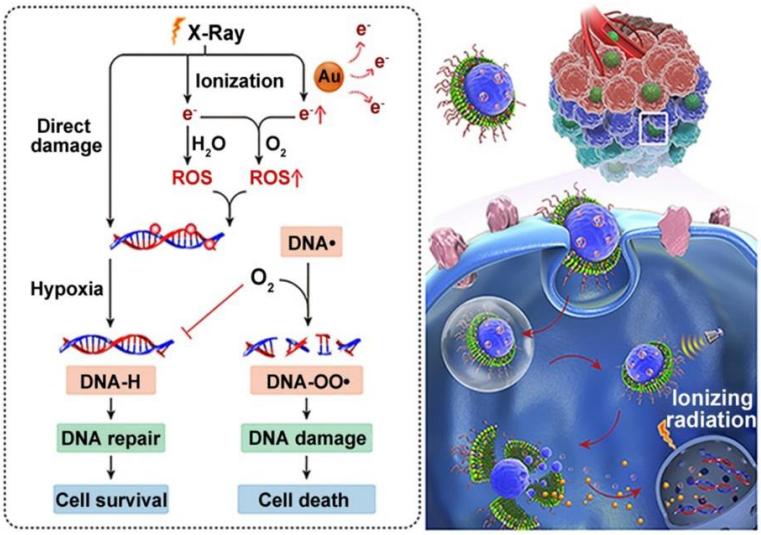

Figure 12. DNA damage induced by radiotherapy (left) mechanism of action of nanodroplets containing ultrasmall AuNPs for cancer radiotherapy (Right). Reprinted with permission from [131].

The outcomes demonstrated that the high metal concentration in tumors required for radiotherapy might be attained using ultrasmall AuNPs. Based on this, Liang *et al*. thoroughly investigated how radiation affected AuNPs of various sizes viz 4.8, 12.1, 27.3, and 46.6 nm PEG-coated AuNPs; their team conducted in-vitro and in-vivo radiosensitization investigations

[15]. 12.1 and 27.3 nm AuNPs were more broadly distributed in cells and had stronger therapeutic benefits than 4.8 and 46.6 nm particles, leading to the tumor virtually disappearing. These experimental findings may be used to choose a better AuNP size for enhancing radiation.

The use of AuNPs in radiotherapy is hampered by a few difficulties, despite the fact that they are clearly advantageous as radiosensitizers. The main problem is selectively targeting AuNPs and removing them quickly to lower radiation exposure and protect healthy tissue [132]. An optimal radiosensitizer will increase tumor retention and significantly improve tumor radiotherapy [133]. According to Fan & Liang *et al*. [134], very efficient cancer treatment uses these particles preferentially aggregated in the tumor via the enhanced permeability and retention effect because of their ultrasmall hydrodynamic diameter and biocompatible surface, which significantly increased radiation effectiveness. In Figure 12, the right part shows the nanodroplets efficiently accumulating at the tumor site, further triggering a rapid release of oxygen and ultrasmall AuNPs upon ultrasound treatment. The left part shows how the ultrasmall AuNPs enhance DNA damage induced by radiotherapy. The oxygen simultaneously relieves tumor hypoxia and fixes the DNA radical intermediates, preventing DNA repair and eventually causing cancer cell death. Following therapy, the kidney could eliminate the extremely small gold nanoclusters from the body, eliminating any potential negative effects brought on by the buildup of gold nanoclusters in the body. This study presents a brand-new and very promising class of radiosensitizers for cancer radiotherapy. It has good qualities, including better tumor accumulation, improved radiation effects, and effective renal clearance. Untargeted radiosensitizers rely on the EPR effect for tumor accumulation, although this method of radiation is still constrained by high quantities of off-target accumulation [135].

5. Limitations

The uses of AuNPs in medicine are restricted even though they provide a number of advantages. The first and most important restriction is the toxicity of the uncapped non-biocompatible AuNPs, which is a serious worry [136]. The composition, shape, size, coating, charge, hydrophobicity, solubility, and reactivity of naked AuNPs are only a few of the factors that affect their toxicity. The varied biological environments, such as biofluids, intracellular media, and inclusion in bio-vesicles, have an impact on the toxicity that AuNPs experience. The second factor restricting their usage in medicine is the development of nanoparticles' characteristics in biological media. According to studies, the naked AuNPs prefer to congregate in lysosomes, changing both their optical characteristics. As a result, the AuNPs require an extra organic or biological surface coating in order to be stable. Even after making biocompatible gold nanoparticles (AuNPs), the most difficult challenge for medical gold nanoformulations is to penetrate biological barriers and specifically recognize their targets. The use of AuNPs in clinical studies and for commercial purposes is restricted by all these restrictions [137].

6. Conclusions

One of the most explored subjects of study on cancer detection and therapy is gold and gold-based nanoparticles because of the uniqueness of gold nanoparticles. Especially for individual and multifold applications such as molecular identification, chemical sensing, and imaging, surface and core characteristics of gold nanoparticles may be optimized. We have portrayed the benefits and medicinal uses of ultrasmall AuNPs, emphasizing cancer treatment. The size effect of AuNPs has been widely researched. Data indicates that ultrasmall AuNPs

enhanced renal clearance, improved tumor tissue permeability, better cell uptake, and more efficient entry into nuclei. Surface modifications and functionalization have been critical in improving the compatibility of ultrasmall AuNPs in physiological environments. To maximize the effectiveness of cancer cell killing and reduce damage to healthy tissues, ultrasmall AuNPs can selectively administer medicines for photodynamic therapy, chemotherapy, gene therapy, and other treatments to tumor tissues. Much work is also needed to minimize the immune system's response to circulating gold nanoparticles to increase their targeting selectivity; strategies to facilitate the efficient clearance of these particles are also a significant challenge. With the transition of gold nanoparticles from the laboratory to human trials, we expect researchers to learn much about the fundamental interactions between nanoscale materials and biological systems. New insights about fundamental biological functions and properties will also be gleaned from their response to exposure to these exotic nanoscale materials. We look forward with great optimism to this new golden age in medicine.

Funding

This research received no external funding.

Acknowledgments

The authors are grateful to the Department of Chemistry, Amity Institute of Applied Sciences, Amity University Uttar Pradesh, India, for allowing them to complete their review by offering the non-teaching credit course (NTCC) in an undergraduate program. The authors are also grateful to Amity University for providing essential library resources for data collection.

Conflicts of Interest

The authors declare no conflict of interest.

References

1. Newsroom, W. Cancer. Available online: https://www.who.int/news-room/fact-sheets/detail/cancer (accessed on 2/01/2023).
2. Kumar, A.; Zhang, X.; Liang, X.-J. Gold nanoparticles: emerging paradigm for targeted drug delivery system. *Biotechnology advances* **2013**, *31*, 593-606, doi:https://doi.org/10.1016/j.biotechadv.2012.10.002.
3. Singh, P.; Pandit, S.; Mokkapati, V.; Garg, A.; Ravikumar, V.; Mijakovic, I. Gold nanoparticles in diagnostics and therapeutics for human cancer. *International journal of molecular sciences* **2018**, *19*, 1979.
4. Heiligtag, F.J.; Niederberger, M. The fascinating world of nanoparticle research. *Materials Today* **2013**, *16*, 262-271, doi:https://doi.org/10.1016/j.mattod.2013.07.004.
5. Chen, H.; Kou, X.; Yang, Z.; Ni, W.; Wang, J. Shape- and Size-Dependent Refractive Index Sensitivity of Gold Nanoparticles. *Langmuir* **2008**, *24*, 5233-5237, doi:10.1021/la800305j.
6. Loo, C.; Lin, A.; Hirsch, L.; Lee, M.-H.; Barton, J.; Halas, N.; West, J.; Drezek, R. Nanoshell-Enabled Photonics-Based Imaging and Therapy of Cancer. *Technology in Cancer Research & Treatment* **2004**, *3*, 33-40, doi:10.1177/153303460400300104.
7. Gong, N.; Chen, S.; Jin, S.; Zhang, J.; Wang, P.C.; Liang, X.-J. Effects of the physicochemical properties of gold nanostructures on cellular internalization. *Regenerative biomaterials* **2015**, *2*, 273-280, doi:https://doi.org/10.1093/rb/rbv024.
8. Gupta, D.; Varghese, B.S.; Suresh, M.; Panwar, C.; Gupta, T.K. Nanoarchitectonics: functional nanomaterials and nanostructures—a review. *Journal of Nanoparticle Research* **2022**, *24*, 196, doi:10.1007/s11051-022-05577-2.
9. Sarfraz, N.; Khan, I. Plasmonic gold nanoparticles (AuNPs): properties, synthesis and their advanced energy, environmental and biomedical applications. *Chemistry–An Asian Journal* **2021**, *16*, 720-742.

10. Huang, K.; Ma, H.; Liu, J.; Huo, S.; Kumar, A.; Wei, T.; Zhang, X.; Jin, S.; Gan, Y.; Wang, P.C. Size-dependent localization and penetration of ultrasmall gold nanoparticles in cancer cells, multicellular spheroids, and tumors in vivo. *ACS nano* **2012**, *6*, 4483-4493.
11. Qazi, Z.; Hassan Baig, M.; Mabood Husain, F.; Yousef Alomar, S.; Dong, J.J.; Sajid Khan, M. Biological reaction mediated engineered AuNPs facilitated delivery encore the anticancer, antiglycation, and antidiabetic potential of garcinol. *Journal of King Saud University - Science* **2023**, *35*, doi:10.1016/j.jksus.2022.102524.
12. Mandal, S. Synthesis of radioactive gold nanoparticle in surfactant medium. *Journal of Radioanalytical and Nuclear Chemistry* **2014**, *299*, 1209-1212, doi:10.1007/s10967-013-2602-z.
13. Wang, Y.X.; Li, A.J.; Wang, H.L.; Liu, W.; Kang, J.; Lu, J.; Lu, S.Y.; Yang, Y.; Liu, K.; Yang, B. *In situ* seed-mediated growth of polymer-grafted gold nanoparticles. *Langmuir* **2019**, *36*, 789-795.
14. Chithrani, D.B.; Jelveh, S.; Jalali, F.; Van Prooijen, M.; Allen, C.; Bristow, R.G.; Hill, R.P.; Jaffray, D.A. Gold nanoparticles as radiation sensitizers in cancer therapy. *Radiation research* **2010**, *173*, 719-728.
15. Zhang, X.D.; Wu, D.; Shen, X.; Chen, J.; Sun, Y.M.; Liu, P.X.; Liang, X.J. Size-dependent radiosensitization of PEG-coated gold nanoparticles for cancer radiation therapy. *Biomaterials* **2012**, *33*, 6408-6419.
16. Schmid, G.; Pfeil, R.; Boese, R.; Bandermann, F.; Meyer, S.; Calis, G.H.; van der Velden, J.W. $Au^{55}[P(C_6H_5)_3]12CI_6$—ein Goldcluster ungewöhnlicher Größe. *Chemische Berichte* **1981**, *114*, 3634-3642.
17. Weare, W.W.; Reed, S.M.; Warner, M.G.; Hutchison, J.E. Improved synthesis of small (d core≈ 1.5 nm) phosphine-stabilized gold nanoparticles. *Journal of the American Chemical Society* **2000**, *122*, 12890-12891.
18. Liu, M.; Wang, J.; Liu, Y.; Lu, R.; Zhang, S. Facile Synthesis of Small Gold Nanoparticles Stabilized by Carbon Nanospheres for Selective Hydrogenation of 4-Nitrobenzaldehyde. *Bulletin of the Korean Chemical Society* **2019**, *40*, 997-1001.
19. Yan, R.; Zhao, Y.; Yang, H.; Kang, X.J.; Wang, C.; Wen, L.L.; Lu, Z.D. Ultrasmall Au Nanoparticles Embedded in 2D Mixed-Ligand Metal–Organic Framework Nanosheets Exhibiting Highly Efficient and Size-Selective Catalysis. *Advanced Functional Materials* **2018**, *28*, 1802021.
20. Murphy, C.J.; Gole, A.M.; Stone, J.W.; Sisco, P.N.; Alkilany, A.M.; Goldsmith, E.C.; Baxter, S.C. Gold nanoparticles in biology: beyond toxicity to cellular imaging. *Accounts of chemical research* **2008**, *41*, 1721-1730.
21. Browning, L.M.; Lee, K.J.; Huang, T.; Nallathamby, P.D.; Lowman, J.E.; Xu, X.-H.N. Random walk of single gold nanoparticles in zebrafish embryos leading to stochastic toxic effects on embryonic developments. *Nanoscale* **2009**, *1*, 138-152.
22. Dauthal, P.; Mukhopadhyay, M. Phyto-synthesis and structural characterization of catalytically active gold nanoparticles biosynthesized using Delonix regia leaf extract. *3 Biotech* **2016**, *6*, 1-9.
23. Noruzi, M.; Zare, D.; Khoshnevisan, K.; Davoodi, D. Rapid green synthesis of gold nanoparticles using Rosa hybrida petal extract at room temperature. *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy* **2011**, *79*, 1461-1465, doi:https://doi.org/10.1016/j.saa.2011.05.001.
24. Siddiqi, K.S.; Husen, A. Recent advances in plant-mediated engineered gold nanoparticles and their application in biological system. *Journal of Trace Elements in Medicine and Biology* **2017**, *40*, 10-23, doi:https://doi.org/10.1016/j.jtemb.2016.11.012.
25. Lee, J.; Kim, H.Y.; Zhou, H.; Hwang, S.; Koh, K.; Han, D.-W.; Lee, J. Green synthesis of phytochemical-stabilized Au nanoparticles under ambient conditions and their biocompatibility and antioxidative activity. *Journal of Materials Chemistry* **2011**, *21*, 13316-13326, doi:10.1039/c1jm11592h.
26. Yang, B.; Chou, J.; Dong, X.; Qu, C.; Yu, Q.; Lee, K.J.; Harvey, N. Size-controlled green synthesis of highly stable and uniform small to ultrasmall gold nanoparticles by controlling reaction steps and pH. *The Journal of Physical Chemistry C* **2017**, *121*, 8961-8967.
27. Yang, B.; Qi, F.; Tan, J.; Yu, T.; Qu, C. Study of green synthesis of ultrasmall gold nanoparticles using *Citrus sinensis* peel. *Applied Sciences* **2019**, *9*, 2423.
28. Manjunath, H.M.; Joshi, C.G.; Raju, N.G. Biofabrication of gold nanoparticles using marine endophytic fungus – *Penicillium citrinum*. *IET Nanobiotechnology* **2017**, *11*, 40-44, doi:https://doi.org/10.1049/iet-nbt.2016.0065.
29. Qu, Y.; Pei, X.; Shen, W.; Zhang, X.; Wang, J.; Zhang, Z.; Li, S.; You, S.; Ma, F.; Zhou, J. Biosynthesis of gold nanoparticles by *Aspergillum* sp. WL-Au for degradation of aromatic pollutants. *Physica E: Low-dimensional Systems and Nanostructures* **2017**, *88*, 133-141, doi:https://doi.org/10.1016/j.physe.2017.01.010.

30. Lee, K.D.; Nagajyothi, P.C.; Sreekanth, T.V.M.; Park, S. Eco-friendly synthesis of gold nanoparticles (AuNPs) using *Inonotus obliquus* and their antibacterial, antioxidant and cytotoxic activities. *Journal of Industrial and Engineering Chemistry* **2015**, *26*, 67-72, doi:https://doi.org/10.1016/j.jiec.2014.11.016.
31. Rangnekar, A.; Sarma, T.K.; Singh, A.K.; Deka, J.; Ramesh, A.; Chattopadhyay, A. Retention of Enzymatic Activity of α-Amylase in the Reductive Synthesis of Gold Nanoparticles. *Langmuir* **2007**, *23*, 5700-5706, doi:10.1021/la062749e.
32. Zhao, P.; Li, N.; Astruc, D. State of the art in gold nanoparticle synthesis. *Coordination Chemistry Reviews* **2013**, *257*, 638-665, doi:https://doi.org/10.1016/j.ccr.2012.09.002.
33. Hu, M.; Chen, J.; Li, Z.Y.; Au, L.; Hartland, G.V.; Li, X.; Marquez, M.; Xia, Y. Gold nanostructures: engineering their plasmonic properties for biomedical applications. *Chemical Society Reviews* **2006**, *35*, 1084-1094, doi:10.1039/b517615h.
34. Turkevich, J.; Stevenson, P.C.; Hillier, J. A study of the nucleation and growth processes in the synthesis of colloidal gold. *Discussions of the Faraday Society* **1951**, *11*, 55-75, doi:10.1039/df9511100055.
35. Frens, G. Controlled Nucleation for the Regulation of the Particle Size in Monodisperse Gold Suspensions. *Nature Physical Science* **1973**, *241*, 20-22, doi:10.1038/physci241020a0.
36. Kimling, J.; Maier, M.; Okenve, B.; Kotaidis, V.; Ballot, H.; Plech, A. Turkevich Method for Gold Nanoparticle Synthesis Revisited. *The Journal of Physical Chemistry B* **2006**, *110*, 15700-15707, doi:10.1021/jp061667w.
37. Herizchi, R.; Abbasi, E.; Milani, M.; Akbarzadeh, A. Current methods for synthesis of gold nanoparticles. *Artificial Cells, Nanomedicine, and Biotechnology* **2016**, *44*, 596-602, doi:10.3109/21691401.2014.971807.
38. Li, C.; Li, D.; Wan, G.; Xu, J.; Hou, W. Facile synthesis of concentrated gold nanoparticles with low size-distribution in water: temperature and pH controls. *Nanoscale Research Letters* **2011**, *6*, 440, doi:10.1186/1556-276x-6-440.
39. Ojea-Jiménez, I.; Bastús, N.G.; Puntes, V. Influence of the Sequence of the Reagents Addition in the Citrate-Mediated Synthesis of Gold Nanoparticles. *The Journal of Physical Chemistry C* **2011**, *115*, 15752-15757, doi:10.1021/jp2017242.
40. Patungwasa, W.; Hodak, J.H. pH tunable morphology of the gold nanoparticles produced by citrate reduction. *Materials Chemistry and Physics* **2008**, *108*, 45-54, doi:https://doi.org/10.1016/j.matchemphys.2007.09.001.
41. Brust, M.; Walker, M.; Bethell, D.; Schiffrin, D.J.; Whyman, R. Synthesis of thiol-derivatised gold nanoparticles in a two-phase Liquid–Liquid system. *Journal of the Chemical Society, Chemical Communications* **1994**, 801-802, doi:10.1039/c39940000801.
42. Darweesh RS; Ayoub NM; Nazzal S. Gold nanoparticles and angiogenesis: molecular mechanisms and biomedical applications. *Int J Nanomedicine.* **2019**, *14*, 7643-7663, doi:https://doi.org/10.2147/IJN.S223941.
43. Kim, K.S.; Demberelnyamba, D.; Lee, H. Size-Selective Synthesis of Gold and Platinum Nanoparticles Using Novel Thiol-Functionalized Ionic Liquids. *Langmuir* **2004**, *20*, 556-560, doi:10.1021/la0355848.
44. Kim, K.S.; Choi, S.; Cha, J.-H.; Yeon, S.-H.; Lee, H. Facile one-pot synthesis of gold nanoparticles using alcohol ionic liquids. *Journal of Materials Chemistry* **2006**, *16*, 1315-1317, doi:10.1039/b601478j.
45. Itoh, H.; Naka, K.; Chujo, Y. Synthesis of Gold Nanoparticles Modified with Ionic Liquid Based on the Imidazolium Cation. *Journal of the American Chemical Society* **2004**, *126*, 3026-3027, doi:10.1021/ja039895g.
46. Park, J.E.; Atobe, M.; Fuchigami, T. Synthesis of multiple shapes of gold nanoparticles with controlled sizes in aqueous solution using ultrasound. *Ultrasonics Sonochemistry* **2006**, *13*, 237-241, doi:https://doi.org/10.1016/j.ultsonch.2005.04.003.
47. Choi, J.; Park, S.; Stojanović, Z.; Han, H.-S.; Lee, J.; Seok, H.K.; Uskoković, D.; Lee, K.H. Facile Solvothermal Preparation of Monodisperse Gold Nanoparticles and Their Engineered Assembly of Ferritin–Gold Nanoclusters. *Langmuir* **2013**, *29*, 15698-15703, doi:10.1021/la403888f.
48. Kobayashi, Y.; Correa-Duarte, M.A.; Liz-Marzán, L.M. Sol−Gel Processing of Silica-Coated Gold Nanoparticles. *Langmuir* **2001**, *17*, 6375-6379, doi:10.1021/la010736p.
49. Bokov, D.; Turki Jalil, A.; Chupradit, S.; Suksatan, W.; Javed Ansari, M.; Shewael, I.H.; Valiev, G.H.; Kianfar, E. Nanomaterial by sol-gel method: synthesis and application. *Advances in Materials Science and Engineering* **2021**, *2021*.

50. Burrows, N.D.; Harvey, S.; Idesis, F.A.; Murphy, C.J. Understanding the Seed-Mediated Growth of Gold Nanorods through a Fractional Factorial Design of Experiments. *Langmuir* **2017**, *33*, 1891-1907, doi:10.1021/acs.langmuir.6b03606.
51. Jenkins, J.A.; Wax, T.J.; Zhao, J. Seed-Mediated Synthesis of Gold Nanoparticles of Controlled Sizes To Demonstrate the Impact of Size on Optical Properties. *Journal of Chemical Education* **2017**, *94*, 1090-1093, doi:10.1021/acs.jchemed.6b00941.
52. Liu, K.; He, Z.; Curtin, J.F.; Byrne, H.J.; Tian, F. A novel, rapid, seedless, in situ synthesis method of shape and size controllable gold nanoparticles using phosphates. *Scientific Reports* **2019**, *9*, 7421, doi:10.1038/s41598-019-43921-0.
53. Gole, A.; Murphy, C.J. Seed-Mediated Synthesis of Gold Nanorods: Role of the Size and Nature of the Seed. *Chemistry of Materials* **2004**, *16*, 3633-3640, doi:10.1021/cm0492336.
54. Bols, P.S.; Anderson, H.L. Template-Directed Synthesis of Molecular Nanorings and Cages. *Accounts of chemical research* **2018**, *51*, 2083-2092, doi:10.1021/acs.accounts.8b00313.
55. Fukuoka, A.; Sakamoto, Y.; Guan, S.; Inagaki, S.; Sugimoto, N.; Fukushima, Y.; Hirahara, K.; Iijima, S.; Ichikawa, M. Novel Templating Synthesis of Necklace-Shaped Mono- and Bimetallic Nanowires in Hybrid Organic−Inorganic Mesoporous Material. *Journal of the American Chemical Society* **2001**, *123*, 3373-3374, doi:10.1021/ja004067y.
56. Palgrave, R.G.; Parkin, I.P. Aerosol Assisted Chemical Vapor Deposition of Gold and Nanocomposite Thin Films from Hydrogen Tetrachloroaurate(III). *Chemistry of Materials* **2007**, *19*, 4639-4647, doi:10.1021/cm0629006.
57. Yan, L.; Wang, F.; Meng, S. Quantum Mode Selectivity of Plasmon-Induced Water Splitting on Gold Nanoparticles. *ACS nano* **2016**, *10*, 5452-5458, doi:10.1021/acsnano.6b01840.
58. Liu, Y.; Williams, M.G.; Miller, T.J.; Teplyakov, A.V. Nanoparticle layer deposition for highly controlled multilayer formation based on high-coverage monolayers of nanoparticles. *Thin Solid Films* **2016**, *598*, 16-24, doi:https://doi.org/10.1016/j.tsf.2015.11.082.
59. Shuang, S.; Zhang, Z. The Effect of Annealing Treatment and Atom Layer Deposition to Au/Pt Nanoparticles-Decorated TiO_2 Nanorods as Photocatalysts. *Molecules* **2018**, *23*, doi:10.3390/molecules23030525.
60. Reetz, M.T.; Helbig, W. Size-Selective Synthesis of Nanostructured Transition Metal Clusters. *Journal of the American Chemical Society* **1994**, *116*, 7401-7402, doi:10.1021/ja00095a051.
61. Reetz, M.T.; Quaiser, S.A. A New Method for the Preparation of Nanostructured Metal Clusters. *Angewandte Chemie International Edition in English* **1995**, *34*, 2240-2241, doi:https://doi.org/10.1002/anie.199522401.
62. Song, Y.Z.; Li, X.; Song, Y.; Cheng, Z.P.; Zhong, H.; Xu, J.M.; Lu, J.S.; Wei, C.G.; Zhu, A.F.; Wu, F.Y.; et al. Electrochemical synthesis of gold nanoparticles on the surface of multi-walled carbon nanotubes with glassy carbon electrode and their application. *Russian Journal of Physical Chemistry A* **2013**, *87*, 74-79, doi:10.1134/s0036024413010275.
63. Huang, C.J.; Chiu, P.H.; Wang, Y.H.; Chen, K.L.; Linn, J.J.; Yang, C.F. Electrochemically Controlling the Size of Gold Nanoparticles. *Journal of The Electrochemical Society* **2006**, *153*, D193, doi:10.1149/1.2358103.
64. Haruta, M.; Daté, M. Advances in the catalysis of Au nanoparticles. *Applied Catalysis A: General* **2001**, *222*, 427-437, doi:https://doi.org/10.1016/S0926-860X(01)00847-X.
65. Jana, N.R.; Gearheart, L.; Murphy, C.J. Seeding Growth for Size Control of 5−40 nm Diameter Gold Nanoparticles. *Langmuir* **2001**, *17*, 6782-6786, doi:10.1021/la0104323.
66. Siti, R.M.; Khairunisak, A.R.; Aziz, A.A.; Noordin, R. Green Synthesis of 10 nm Gold Nanoparticles via Seeded-Growth Method and its Conjugation Properties on Lateral Flow Immunoassay. *Advanced Materials Research* **2013**, *686*, 8-12, doi:10.4028/www.scientific.net/AMR.686.8.
67. Elia, P.; Zach, R.; Hazan, S.; Kolusheva, S.; Porat, Z.; Zeiri, Y. Green synthesis of gold nanoparticles using plant extracts as reducing agents. *Int J Nanomedicine.* **2014**, *9*, 4007-4021, doi:https://doi.org/10.2147/IJN.S57343.
68. Singh, M.; Kalaivani, R.; Manikandan, S.; Sangeetha, N.; Kumaraguru, A.K. Facile green synthesis of variable metallic gold nanoparticle using *Padina gymnospora*, a brown marine macroalga. *Applied Nanoscience* **2013**, *3*, 145-151, doi:10.1007/s13204-012-0115-7.
69. Husseiny, M.I.; El-Aziz, M.A.; Badr, Y.; Mahmoud, M.A. Biosynthesis of gold nanoparticles using *Pseudomonas aeruginosa*. *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy* **2007**, *67*, 1003-1006, doi:https://doi.org/10.1016/j.saa.2006.09.028.

70. Shankar, S.S.; Rai, A.; Ahmad, A.; Sastry, M. Rapid synthesis of Au, Ag, and bimetallic Au core–Ag shell nanoparticles using Neem (*Azadirachta indica*) leaf broth. *Journal of Colloid and Interface Science* **2004**, *275*, 496-502, doi:https://doi.org/10.1016/j.jcis.2004.03.003.
71. Chandran, S.P.; Chaudhary, M.; Pasricha, R.; Ahmad, A.; Sastry, M. Synthesis of Gold Nanotriangles and Silver Nanoparticles Using *Aloe vera* Plant Extract. *Biotechnology Progress* **2006**, *22*, 577-583, doi:https://doi.org/10.1021/bp0501423.
72. Gardea-Torresdey, J.L.; Parsons, J.G.; Gomez, E.; Peralta-Videa, J.; Troiani, H.E.; Santiago, P.; Yacaman, M.J. Formation and Growth of Au Nanoparticles inside Live Alfa alfa Plants. *Nano letters* **2002**, *2*, 397-401, doi:10.1021/nl015673+.
73. Huang, J.; Li, Q.; Sun, D.; Lu, Y.; Su, Y.; Yang, X.; Wang, H.; Wang, Y.; Shao, W.; He, N.; et al. Biosynthesis of silver and gold nanoparticles by novel sun dried *Cinnamomum camphora* leaf. *Nanotechnology* **2007**, *18*, 105104, doi:10.1088/0957-4484/18/10/105104.
74. Smitha, S.; Philip, D.; Gopchandran, K. Green synthesis of gold nanoparticles using *Cinnamomum zeylanicum* leaf broth. *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy* **2009**, *74*, 735-739.
75. Parida, U.K.; Bindhani, B.K.; Nayak, P. Green synthesis and characterization of gold nanoparticles using onion (*Allium cepa*) extract. *World J Nano Sci Eng* **2011**, *1*, 93.
76. Pearce, K.; Thipe, V.C.; Henkel, R.R.; Katti, K.V. Green Nanotechnology as an innovative drug delivery approach for *Typha capensis* and *Naringenin*—New class of phytochemical embedded biocompatible gold nanoparticles in prostate cancer therapy. *Journal of Drug Delivery Science and Technology* **2023**, *80*, doi:10.1016/j.jddst.2022.104100.
77. Rezk, N.; Abdelsattar, A.S.; Makky, S.; Hussein, A.H.; Kamel, A.G.; El-Shibiny, A. New formula of the green synthesised Au@Ag core@shell nanoparticles using propolis extract presented high antibacterial and anticancer activity. *AMB Express* **2022**, *12*, doi:10.1186/s13568-022-01450-6.
78. Shirzadi-Ahodashti, M.; Mizwari, Z.M.; Mohammadi-Aghdam, S.; Ahmadi, S.; Ali Ebrahimzadeh, M.; Mortazavi-Derazkola, S. Optimization and evaluation of anticancer, antifungal, catalytic, and antibacterial activities: Biosynthesis of spherical-shaped gold nanoparticles using Pistacia vera hull extract (AuNPs@PV). *Arabian Journal of Chemistry* **2023**, *16*, doi:10.1016/j.arabjc.2022.104423.
79. Parthiban, A.; Sachithanandam, V.; Sarangapany, S.; Misra, R.; Muthukrishnan, P.; Jeyakumar, T.C.; Purvaja, R.; Ramesh, R. Green synthesis of gold nanoparticles using quercetin biomolecule from mangrove plant, Ceriops tagal: Assessment of antiproliferative properties, cellular uptake and DFT studies. *Journal of Molecular Structure* **2023**, *1272*, doi:10.1016/j.molstruc.2022.134167.
80. Lin, X.; Yu, Y.; Wang, X.; Goorani, S. Green synthesis, chemical characterization of gold nanoparticles decorated on biodegradable arabic gum modified magnetic nanoparticles for the treatment of leukemia. *Inorganic Chemistry Communications* **2022**, *146*, doi:10.1016/j.inoche.2022.110171.
81. Huang, W.; Chen, S.; Liu, Y.; Fu, H.; Wu, G. The controlled synthesis of stable gold nanoparticles in quaternary ammonium ionic liquids by simple heating. *Nanotechnology* **2011**, *22*, 025602, doi:10.1088/0957-4484/22/2/025602.
82. Cao, X.; Koltypin, Y.; Kataby, G.; Prozorov, R.; Gedanken, A. Controlling the particle size of amorphous iron nanoparticles. *Journal of Materials Research* **1995**, *10*, 2952-2957, doi:10.1557/jmr.1995.2952.
83. Fujimoto, T.; Terauchi, S.-y.; Umehara, H.; Kojima, I.; Henderson, W. Sonochemical Preparation of Single-Dispersion Metal Nanoparticles from Metal Salts. *Chemistry of Materials* **2001**, *13*, 1057-1060, doi:10.1021/cm000910f.
84. Okitsu, K.; Mizukoshi, Y.; Bandow, H.; Maeda, Y.; Yamamoto, T.; Nagata, Y. Formation of noble metal particles by ultrasonic irradiation. *Ultrasonics Sonochemistry* **1996**, *3*, S249-S251, doi:https://doi.org/10.1016/S1350-4177(96)00033-8.
85. Yeung, S.A.; Hobson, R.; Biggs, S.; Grieser, F. Formation of gold sols using ultrasound. *Journal of the Chemical Society, Chemical Communications* **1993**, 378-379, doi:10.1039/c39930000378.
86. Nagata, Y.; Mizukoshi, Y.; Okitsu, K.; Maeda, Y. Sonochemical Formation of Gold Particles in Aqueous Solution. *Radiation research* **1996**, *146*, 333-338, doi:10.2307/3579465.
87. Caruso, R.A.; Ashokkumar, M.; Grieser, F. Sonochemical Formation of Gold Sols. *Langmuir* **2002**, *18*, 7831-7836, doi:10.1021/la020276f.
88. Fuentes-García, J.A.; Santoyo-Salzar, J.; Rangel-Cortes, E.; Goya, G.F.; Cardozo-Mata, V.; Pescador-Rojas, J.A. Effect of ultrasonic irradiation power on sonochemical synthesis of gold nanoparticles. *Ultrasonics Sonochemistry* **2021**, *70*, 105274, doi:https://doi.org/10.1016/j.ultsonch.2020.105274.

89. Chen, W.; Cai, W.; Zhang, L.; Wang, G.; Zhang, L. Sonochemical Processes and Formation of Gold Nanoparticles within Pores of Mesoporous Silica. *Journal of Colloid and Interface Science* **2001**, *238*, 291-295, doi:https://doi.org/10.1006/jcis.2001.7525.
90. Jin, Y.; Wang, P.; Yin, D.; Liu, J.; Qin, L.; Yu, N.; Xie, G.; Li, B. Gold nanoparticles prepared by sonochemical method in thiol-functionalized ionic liquid. *Colloids and Surfaces A: Physicochemical and Engineering Aspects* **2007**, *302*, 366-370, doi:https://doi.org/10.1016/j.colsurfa.2007.02.060.
91. Amendola, V.; Rizzi, G.A.; Polizzi, S.; Meneghetti, M. Synthesis of Gold Nanoparticles by Laser Ablation in Toluene: Quenching and Recovery of the Surface Plasmon Absorption. *The Journal of Physical Chemistry B* **2005**, *109*, 23125-23128, doi:10.1021/jp055783v.
92. Li, H.; Yue, X.; Gao, N.; Tang, J.; Lv, X.; Hou, J. Microwave method synthesis of magnetic ionic liquid/gold nanoparticles as ultrasensitive SERS substrates for trace clopidol detection. *Analytical and Bioanalytical Chemistry* **2020**, *412*, 3063-3071, doi:10.1007/s00216-020-02588-7.
93. Albanese, A.; Chan, W.C. Effect of gold nanoparticle aggregation on cell uptake and toxicity. *ACS nano* **2011**, *5*, 5478-5489.
94. Oh, N.; Park, J.-H. Endocytosis and exocytosis of nanoparticles in mammalian cells. *International journal of nanomedicine* **2014**, *9*, 51.
95. Vácha, R.; Martinez-Veracoechea, F.J.; Frenkel, D. Receptor-mediated endocytosis of nanoparticles of various shapes. *Nano letters* **2011**, *11*, 5391-5395.
96. Kumar, A.; Ma, H.; Zhang, X.; Huang, K.; Jin, S.; Liu, J.; Wei, T.; Cao, W.; Zou, G.; Liang, X.J. Gold nanoparticles functionalized with therapeutic and targeted peptides for cancer treatment. *Biomaterials* **2012**, *33*, 1180-1189.
97. Loynachan, C.N.; Soleimany, A.P.; Dudani, J.S.; Lin, Y.; Najer, A.; Bekdemir, A.; Chen, Q.; Bhatia, S.N.; Stevens, M.M. Renal clearable catalytic gold nanoclusters for in vivo disease monitoring. *Nature nanotechnology* **2019**, *14*, 883-890.
98. Sokolova, V.; Mekky, G.; van der Meer, S.B.; Seeds, M.C.; Atala, A.J.; Epple, M. Transport of ultrasmall gold nanoparticles (2 nm) across the blood–brain barrier in a six-cell brain spheroid model. *Scientific Reports* **2020**, *10*, 1-12.
99. Bailly, A.-L.; Correard, F.; Popov, A.; Tselikov, G.; Chaspoul, F.; Appay, R.; Al-Kattan, A.; Kabashin, A.V.; Braguer, D.; Esteve, M.-A. In vivo evaluation of safety, biodistribution and pharmacokinetics of laser-synthesized gold nanoparticles. *Scientific Reports* **2019**, *9*, 1-12.
100. Bahrami, B.; Hojjat-Farsangi, M.; Mohammadi, H.; Anvari, E.; Ghalamfarsa, G.; Yousefi, M.; Jadidi-Niaragh, F. Nanoparticles and targeted drug delivery in cancer therapy. *Immunology letters* **2017**, *190*, 64-83.
101. Thakuria, A.; Kataria, B.; Gupta, D. Nanoparticle-based methodologies for targeted drug delivery—an insight. *Journal of Nanoparticle Research* **2021**, *23*, 87, doi:10.1007/s11051-021-05190-9.
102. Ajnai, G.; Chiu, A.; Kan, T.; Cheng, C.-C.; Tsai, T.-H.; Chang, J. Trends of gold nanoparticle-based drug delivery system in cancer therapy. *Journal of Experimental & Clinical Medicine* **2014**, *6*, 172-178.
103. Cobley, C.M.; Chen, J.; Cho, E.C.; Wang, L.V.; Xia, Y. Gold nanostructures: a class of multifunctional materials for biomedical applications. *Chemical Society Reviews* **2011**, *40*, 44-56.
104. Chen, Y.-H.; Tsai, C.-Y.; Huang, P.-Y.; Chang, M.-Y.; Cheng, P.-C.; Chou, C.-H.; Chen, D.-H.; Wang, C.-R.; Shiau, A.-L.; Wu, C.-L. Methotrexate conjugated to gold nanoparticles inhibits tumor growth in a syngeneic lung tumor model. *Molecular pharmaceutics* **2007**, *4*, 713-722.
105. Wang F; Wang YC; Dou S; Xiong MH; Sun TM; J., W. Doxorubicin-tethered responsive gold nanoparticles facilitate intracellular drug delivery for overcoming multidrug resistance in cancer cells. *ACS nano* **2011**, 3679-3692, doi:doi: 10.1021/nn200007z.
106. Kong, F.-Y.; Zhang, J.-W.; Li, R.-F.; Wang, Z.-X.; Wang, W.-J.; Wang, W. Unique roles of gold nanoparticles in drug delivery, targeting and imaging applications. *Molecules* **2017**, *22*, 1445.
107. Emami, F.; Banstola, A.; Vatanara, A.; Lee, S.; Kim, J.O.; Jeong, J.-H.; Yook, S. Doxorubicin and anti-PD-L1 antibody conjugated gold nanoparticles for colorectal cancer photochemotherapy. *Molecular pharmaceutics* **2019**, *16*, 1184-1199.
108. Steckiewicz, K.P.; Barcinska, E.; Malankowska, A.; Zauszkiewicz–Pawlak, A.; Nowaczyk, G.; Zaleska-Medynska, A.; Inkielewicz-Stepniak, I. Impact of gold nanoparticles shape on their cytotoxicity against human osteoblast and osteosarcoma in *in-vitro* model. Evaluation of the safety of use and anticancer potential. *Journal of Materials Science: Materials in Medicine* **2019**, *30*, 1-15.

109. Huo, S.; Ma, H.; Huang, K.; Liu, J.; Wei, T.; Jin, S.; Zhang, J.; He, S.; Liang, X.J. Superior Penetration and Retention Behavior of 50 nm Gold Nanoparticles in TumorsCell Penetration and Tumor Retention of Gold Nanoparticles. *Cancer research* **2013**, *73*, 319-330.
110. Suk JS; Xu Q; Kim N; Hanes J; Ensign LM. PEGylation as a strategy for improving nanoparticle-based drug and gene delivery. *Adv Drug Deliv Rev.* **2016**, *99(Pt A)*, 28-51, doi:doi: 10.1016/j.addr.2015.09.012.
111. Schöttler, S.; Becker, G.; Winzen, S.; Steinbach, T.; Mohr, K.; Landfester, K.; Mailänder, V.; Wurm, F.R. Protein adsorption is required for stealth effect of poly (ethylene glycol)-and poly (phosphoester)-coated nanocarriers. *Nature nanotechnology* **2016**, *11*, 372-377.
112. Boisselier, E.; Astruc, D. Gold nanoparticles in nanomedicine: preparations, imaging, diagnostics, therapies and toxicity. *Chemical Society Reviews* **2009**, *38*, 1759-1782.
113. Zhang, X.D.; Wu, D.; Shen, X.; Liu, P.X.; Fan, F.Y.; Fan, S.J. *In vivo* renal clearance, biodistribution, toxicity of gold nanoclusters. *Biomaterials* **2012**, *33*, 4628-4638.
114. Singh, P.; Pandit, S.; Mokkapati, V.R.S.S.; Garg, A.; Ravikumar, V.; Mijakovic, I. Gold Nanoparticles in Diagnostics and Therapeutics for Human Cancer. *International journal of molecular sciences* **2018**, *19*, 1979, doi:https://doi.org/10.3390/ijms19071979.
115. Lee, K.; Lee, H.; Bae, K.H.; Park, T.G. Heparin immobilized gold nanoparticles for targeted detection and apoptotic death of metastatic cancer cells. *Biomaterials* **2010**, *31*, 6530-6536.
116. You, J.; Zhang, G.; Li, C. Exceptionally High Payload of Doxorubicin in Hollow Gold Nanospheres for Near-Infrared Light-Triggered Drug Release. *ACS nano* **2010**, *4*, 1033-1041, doi:10.1021/nn901181c.
117. Raghvendra, R.; Kanthadeivi, A.; Sathesh, K.; Aarrthy, M. Diagnostics and therapeutic application of gold nanoparticles. *International Journal of Pharmacy and Pharmaceutical Sciences* **2014**, *6*, 4.
118. D'Acunto, M.; Cioni, P.; Gabellieri, E.; Presciuttini, G. Exploiting gold nanoparticles for diagnosis and cancer treatments. *Nanotechnology* **2021**, *32*, 192001, doi:10.1088/1361-6528/abe1ed.
119. Gupta N; Malviya R. Understanding and advancement in gold nanoparticle targeted photothermal therapy of cancer. *Biochim Biophys Acta Rev Cancer*. **2021**, *Apr;1875*, 188532, doi: doi: 10.1016/j.bbcan.2021.188532.
120. Nejabat, M.; Samie, A.; Ramezani, M.; Alibolandi, M.; Abnous, K.; Taghdisi, S.M. An Overview on Gold Nanorods as Versatile Nanoparticles in Cancer Therapy. *Journal of Controlled Release* **2023**, *354*, 221-242, doi:10.1016/j.jconrel.2023.01.009.
121. Faid, A.H.; Shouman, S.A.; Badr, Y.A.; Sharaky, M. Enhanced photothermal heating and combination therapy of gold nanoparticles on a breast cell model. *BMC Chemistry* **2022**, *16*, doi:10.1186/s13065-022-00859-1.
122. Kumar, A.; Huo, S.; Zhang, X.; Liu, J.; Tan, A.; Li, S.; Jin, S.; Xue, X.; Zhao, Y.; Ji, T. Neuropilin-1-targeted gold nanoparticles enhance therapeutic efficacy of platinum (IV) drug for prostate cancer treatment. *ACS nano* **2014**, *8*, 4205-4220.
123. Baptista, M.S.; Cadet, J.; Di Mascio, P.; Ghogare, A.A.; Greer, A.; Hamblin, M.R.; Lorente, C.; Nunez, S.C.; Ribeiro, M.S.; Thomas, A.H. Type I and type II photosensitized oxidation reactions: guidelines and mechanistic pathways. *Photochemistry and photobiology* **2017**, *93*, 912-919.
124. Cheng, Y.; Samia, A.C.; Meyers, J.D.; Panagopoulos, I.; Fei, B.; Burda, C. Highly efficient drug delivery with gold nanoparticle vectors for *in vivo* photodynamic therapy of cancer. *Journal of the American Chemical Society* **2008**, *130*, 10643-10647, doi:https://doi.org/10.1021/ja801631c.
125. Han, Y.; Chen, Z.; Zhao, H.; Zha, Z.; Ke, W.; Wang, Y.; Ge, Z. Oxygen-independent combined photothermal/photodynamic therapy delivered by tumor acidity-responsive polymeric micelles. *Journal of Controlled Release* **2018**, *284*, 15-25, doi:https://doi.org/10.1016/j.jconrel.2018.06.012.
126. Hone, D.C.; Walker, P.I.; Evans-Gowing, R.; FitzGerald, S.; Beeby, A.; Chambrier, I.; Cook, M.J.; Russell, D.A. Generation of cytotoxic singlet oxygen via phthalocyanine-stabilized gold nanoparticles: a potential delivery vehicle for photodynamic therapy. *Langmuir* **2002**, *18*, 2985-2987, doi:http://dx.doi.org/10.1021/la0256230.
127. Camerin, M.; Magaraggia, M.; Soncin, M.; Jori, G.; Moreno, M.; Chambrier, I.; Cook, M.J.; Russell, D.A. The *in vivo* efficacy of phthalocyanine–nanoparticle conjugates for the photodynamic therapy of amelanotic melanoma. *European journal of cancer* **2010**, *46*, 1910-1918, doi:https://doi.org/10.1016/j.ejca.2010.02.037.
128. Kuo, W.S.; Chang, C.N.; Chang, Y.T.; Yang, M.H.; Chien, Y.H.; Chen, S.J.; Yeh, C.S. Gold nanorods in photodynamic therapy, as hyperthermia agents, and in near-infrared optical imaging. *Angewandte Chemie* **2010**, *122*, 2771-2775, doi: https://doi.org/10.1002/anie.200906927.

129. Kuo, W.S.; Chang, Y.T.; Cho, K.C.; Chiu, K.C.; Lien, C.H.; Yeh, C.S.; Chen, S.J. Gold nanomaterials conjugated with indocyanine green for dual-modality photodynamic and photothermal therapy. *Biomaterials* **2012**, *33*, 3270-3278, doi:https://doi.org/10.1016/j.biomaterials.2012.01.035.
130. Hainfeld, J.F.; Slatkin, D.N.; Smilowitz, H.M. The use of gold nanoparticles to enhance radiotherapy in mice. *Physics in Medicine & Biology* **2004**, *49*, N309, doi:https://doi.org/10.1088/0031-9155/49/18/n03.
131. Jiang, W.; Li, Q.; Xiao, L.; Dou, J.; Liu, Y.; Yu, W.; Ma, Y.; Li, X.; You, Y.-Z.; Tong, Z.; *et al*. Hierarchical Multiplexing Nanodroplets for Imaging-Guided Cancer Radiotherapy via DNA Damage Enhancement and Concomitant DNA Repair Prevention. *ACS Nano* **2018**, *12*, 5684-5698, doi:10.1021/acsnano.8b01508.
132. Luo, D.; Wang, X.; Zeng, S.; Ramamurthy, G.; Burda, C.; Basilion, J.P. Targeted gold nanocluster-enhanced radiotherapy of prostate cancer. *Small* **2019**, *15*, 1900968, doi:https://doi.org/10.1002/smll.201900968.
133. Zhang, Y.; Huang, F.; Ren, C.; Liu, J.; Yang, L.; Chen, S.; Chang, J.; Yang, C.; Wang, W.; Zhang, C. Enhanced radiosensitization by gold nanoparticles with acid-triggered aggregation in cancer radiotherapy. *Advanced Science* **2019**, *6*, 1801806, doi:https://doi.org/10.1002%2Fadvs.201801806.
134. Fan, M.; Han, Y.; Gao, S.; Yan, H.; Cao, L.; Li, Z.; Liang, X.-J.; Zhang, J. Ultrasmall gold nanoparticles in cancer diagnosis and therapy. *Theranostics* **2020**, *10*, 4944, doi:https://doi.org/10.7150/thno.42471.
135. Zhang, X.D.; Chen, J.; Luo, Z.; Wu, D.; Shen, X.; Song, S.S.; Sun, Y.M.; Liu, P.X.; Zhao, J.; Huo, S. Enhanced tumor accumulation of sub-2 nm gold nanoclusters for cancer radiation therapy. *Advanced healthcare materials* **2014**, *3*, 133-141, doi:https://doi.org/10.1002/adhm.201300189.
136. Gupta, D.; Yadav, P.; Garg, D.; Gupta, T.K. Pathways of nanotoxicity: Modes of detection, impact, and challenges. *Frontiers of Materials Science* **2021**, *15*, 512-542, doi:10.1007/s11706-021-0570-8.
137. Feliu, N.; Docter, D.; Heine, M.; Del Pino, P.; Ashraf, S.; Kolosnjaj-Tabi, J.; Macchiarini, P.; Nielsen, P.; Alloyeau, D.; Gazeau, F. *In vivo* degeneration and the fate of inorganic nanoparticles. *Chemical Society Reviews* **2016**, *45*, 2440-2457, doi:https://doi.org/10.1039/C5CS00699F.