REVIEW PAPER

Current perspective on theranostic gold nanoparticles: Synthesis and biomedical applications

Mohammad Ali Farzin [1], Hassan Abdoos [1] , Reza Saber [2]

[1]Department of Nanotechnology, Faculty of New Sciences and Technologies, Semnan University, Semnan, Iran
[2]Department of Medical Nanotechnology, School of Advanced Technologies in Medicine, Tehran University of Medical Sciences, Tehran, Iran

ABSTRACT

As one of the most well-known metal nanoparticles, gold nanoparticles (AuNPs) have attracted much attention for the biological applications. This great interest in AuNPs can be attributed to their outstanding physical and chemical properties, such as special optical and electrochemical characteristics, high X-ray attenuation ability, strong X-ray absorption, photothermal effect, stability and biocompatibility. In addition, due to the ease of synthesis and modification of the surface of AuNPs, it is possible to control their shape, size and surface characteristics. All these features suggest that AuNPs can be used for biosensing strategies, drug delivery, photothermal therapy, nanobrachytherapy, enhanced radiotherapy and CT imaging. In addition, they can be used as antibacterial and antifungal agents. This minireview focuses on the key principles, research achievements and new opportunities in the synthesis of AuNPs as well as their biological applications. In fact, the growing progress in the use of AuNPs for the diagnostic and therapeutic applications is described in this survey. Overall, a better understanding of the key aspects of the synthesis methodologies will lead to the development of new protocols that can provide ideas for more cost-effective and reliable approaches to the production of AuNPs.

Keywords: *AuNPs, Diagnosis, Synthesis, Therapy*

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INTRODUCTION

Nanotechnology is the golden treasure whose discovery changed the lives of many people. A market that is estimated to reach a value of 124 billion dollars by 2024 [1]. The significant development of nanotechnology in different aspects has caused the widespread use of nanoparticles in various fields, especially in biology and medicine. In the meantime, gold nanoparticles (AuNPs) have attracted a lot of attention due to their unique characteristics based on their biocompatibility, surface and physicochemical properties [2-4]. In addition, they have easy preparation, and are non toxic [2]. AuNPs can be synthesized in the various shapes such as nanospheres, nanoflowers, nanorods, nanowires, nanostars, nanocages and nanocubes [5].

* *Corresponding author: Email: h.abdoos@semnan.ac.ir*
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Among different metal nanoparticles, AuNPs have the least toxicity, as a result, they are more suitable for biological/medical applications. However, their low clearance rate from the bloodstream and tissues may cause health problems. For biological applications, these nanoparticles can be modified with biomolecules such as antibodies, proteins, enzymes, nucleic acids (DNA or RNA) and drugs [6].

Surface engineering can precisely control and adjust the surface properties of AuNPs for biological purposes. Surface chemistry gives AuNPs the ability to conjugate with biomolecules through electrostatic interaction and self-assembly of covalent bonds between gold particles and thiol groups [7]. Compared to the common techniques of functionalizing nanomaterials, the method of conjugating AuNPs (self-assemble covalent bond) is simpler and less expensive and is effective in binding bioreceptors vertically on the gold surface. Due to direct surface functionalization and excellent

biocompatibility, AuNPs do not induce unwanted immune response [7].

AuNPs possess unique and tunable optical characteristics. The optical properties of AuNPs depend on surface plasmon resonance (SPR) [5]. The interaction of the oscillating electric fields of the light beam of AuNPs with free electrons leads to the coordinated oscillation of the electron charge of gold particles, which resonate with the frequency of visible light. These resonant oscillations are known as SPR. The surface plasmon resonance can be tuned by changing the size or shape of the nanoparticles, which leads to the creation of particles with suitable optical properties for various applications [5, 8].

In recent years, the production of core-shell AuNPs has been the interest of many researchers in various fields, due to the core activity with unique properties and surface modification by a shell. Features and distinctive properties including physicochemical, electrochemical, biological, optical, etc. can be observed when AuNPs are synthesized in core-shell form. For example, the assembling N-doped carbon dots (N-CDs) on AuNPs leads to the aggregation of nanoparticles. Cysteine penetrates into the hybrid N-CD shell and leads the dispersion of aggregated core-shell AuNPs, which results in the color change from purple to red and the luminescence recovery of CDs. This method was successfully used to detect cysteine in human serum [9].

This minireview focuses on recent developments in the field of AuNPs from synthesis methods to biological applications. In the section of applications, it reviews key processes in AuNPs-based diagnosis and treatment of diseases with emphasis on eight strategies, namely, sensing, drug delivery, photothermal therapy, theranostic radiopharmacy, nanobrachytherapy, immunotherapy, nanoparticle-enhanced radiotherapy, CT imaging and also antimicrobial activities of AuNPs. Overall, this article provides an accurate roadmap that can be used by biological researchers when attempting to bridge the gap between material science and biomedicine.

Current methods for synthesis of AuNPs

The synthesis of metal nanoparticles in desired shapes and dimensions is considered as one of the important aspects of nanotechnology. There are two strategies for the production of AuNPs including bottom-up and top-down approaches. The bottom-up approach refers to the synthesis of nanoparticles using chemical reactions between atoms/ions. While the top-down strategy cracks bulk materials into nanoparticles using different methods. The top-down approach includes pulsed laser ablation, vacuum sputtering and arc discharge; whereas the reduction of Au(III) to Au(0) is the bottom-up approach. Top-down methods are best suited for producing nanomaterals with long-range order and for making macroscopic connections. While bottom-up strategies are suitable for assembly and creating short-range order at nanoscale dimensions. It is expected that the combination of bottom-up and top-down techniques will ultimately be the best way for fabdication of nanoparticles.

Bottom-up approach

In the bottom-up method, nanomaterials are produced by joining together building blocks such as atoms. One of the most important advantages of this method is the possibility of less waste and, as a result, it is more economical. Despite these advantages, this method tends to create internal stress and hence increases the possibility of defects and surface contamination [10].

Chemical method

Classical methods for the synthesis of metal nanoparticles are based on the chemical reduction of the corresponding cations using appropriate reagents, which play the dual role of reducing and stabilizing. The presence of a stabilizing layer on the nascent particle is necessary to prevent its infinite growth.

For the first time, Faraday synthesized colloidal gold using chloroauric acid ($HAuCl_4$) as the source of gold and phosphorus vapour reducer. This aqueous gold salt solution is still the most widely used precursor for the bottom-up synthesis of AuNPs. Phosphorus, originally used by Faraday, is still utilized to prepare colloids with an average diameter of 3 to 12 nm.

Turkevich used sodium citrate as a reducing agent for the first time in 1951 [11]. Turkevich's method is based on adding sodium citrate to a boiling aqueous solution of HAuCl4 (Au3+ ions), which is accompanied by the production of red AuNPs (Fig. 1). In his procedure, the citrate ions play a double role, as both stabilizing and reducing agents. In this method, the sizes of AuNPs can change by varying the concentration

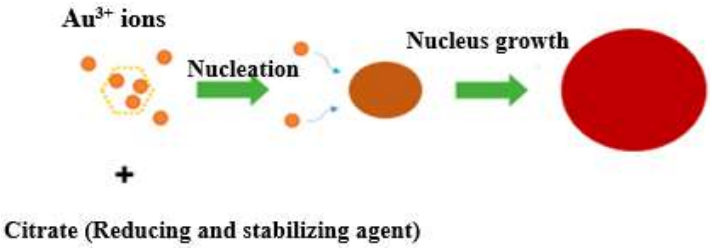

Fig. 1. Scheme of Turkevich method for AuNP synthesis

of sodium citrate. Kimling and co-workers showed that high concentrations of citrate lead to faster stabilization of AuNPs with smaller sizes, while low concentrations of citrate lead to aggregation of small particles into larger particles [12]. This method refined by Frens in 1970s, is the simplest available one [13].

In the chemical production of AuNPs, the Turkevich's approach is a promising method compared to other methods. The main limitation of this method is the need for precise control of concentration, temperature and pH, which must be strictly observed to produce monodisperse particles with optimal sizes [14]. Thus, attention is given to overcome limitations of Turkevich's method by optimizing the reaction medium.

Besides sodium citrate, sodium borohydride (NaBH4) is also one of the most common chemical reducers for chemical synthesis of AuNPs. The sodium borohydride yields highly concentrated nanoparticles because it increases the overall ionic strength [15].

Seed-mediated growth method

In this method, small seeds are first produced through the reduction of Au(III) ions by a strong reducer and then grown into large particles using a mild reducing agent. To prevent added nucleation, seed particles are immersed in a metal salt solution containing a structure-directing agent and a mild reducing agent. In this method, the geometry of Au nanomaterials changes by changing the reducing agents, concentration of seeds and structure-directing agents [16].

Green synthetic methods

Although the chemical methods are the most common approaches for the synthesis of AuNPs, the use of expensive and toxic reagents limits their biological applications [17]. To overcome the limitatios of chemical approaches, biological and natural materials linked with Au(III) to produce nanoparticles. Green synthesis compared to the traditional chemical synthesis is more beneficial because it decreases pollution, costs less and improves environmental safety and and human health. Despite all the advantages of green synthesis of AuNPs, this strategy suffers from some limitations. The disadvantage of using natural or biological reagents for the synthesis of AuNPs is that it is difficult to identify the reactive components because plant biomass or microorganisms contain a large number of organic components [18, 19]. Another limitation of the green synthesis of AuNPs is its low efficiency in the production of nanoparticles. In addition, a major drawback of green synthesis of nanoparticles is the reaction time, which can vary up to several days compared to chemical and physical synthesis that takes several minutes or hours [20].

Green synthesis by plants/algae

Green methods can be attributed to the synthesis of metal nanoparticles using plants or plant parts or using their extracts. It has been known for a long time that plants can reduce metal ions both on their surface and in various organs and tissues away from the site of ion penetration. It is interesting to note that the study of the bioaccumulation process of metals in plants has shown that metal ions are usually deposited in the form of nanoparticles [21].

There are various plants that can be utilized to reduce and stabilize the metallic nanoparticles. Tabrizi and co-workers developed the green synthesis process of AuNPs using the aqueous extract of rose flower (rose water) as the reducing and stabilizing agent [22]. In another study, Ghosh et al. synthesized AuNPs using *Gnidia glauca* flower extract [23]. The green synthesis of AuNPs also was described by Li and co-workers using the of *Mentha Longifolia* leaf extract [24]. These researchers investigat the anti-breast carcinoma properties of as-prepared AuNPs in the *in vitro* condition.

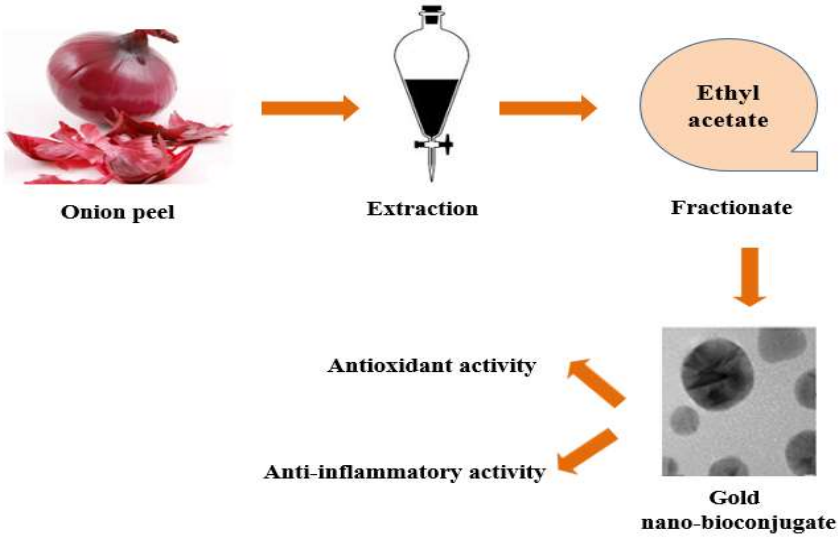

Fig. 2 Experimental design of the protocol followed for extraction of ethyl acetate from onion peel and a green method adopted for preparation of gold nano-bioconjugates and studying antioxidant and anti-inflammatory activities

Fruit and vegetable peels, which are usually considered as a waste material, contain many chemical components including minerals, proteins, vitamins, lipids, flavonoids and carotenoids, and phenolic compounds, which act as reductants and nanoparticle stabilizers. For example, AuNPs were synthesized using pineapple peel and passion fruit peel extracts [25]. In another study, the ethyl acetate fraction of onion peel extract was utilizd for the synthesis of AuNPs with the antioxidant and anti-inflammatory activity [26](Fig. 2).

In recent years, a relatively new trend has been observed for the rapid and valuable synthesis of nanoparticles from algae (living or dead), which can be attributed to the widespread presence of algae in the Earth's crust and their unique properties, such as fast propagation and capacity of accumulation and reduction of metallic ions [27]. For example, the extracellular AuNPs were synthesized using the aqueous extract of the brown algae *Laminaria japonica* [28]. In another study, the synthesis of AuNPs using crude fucoidan from the invasive brown seaweed *Sargassum muticum* was developed by González-Ballesteros et al. [29].

Green synthesis by biological materials

Biological synthesis (biosynthesis) of nanoparticles as an eco-friendly and green method has been at the center of attention in current years. In biological methods, nanoparticles are produced by enzymes, microorganisms, biopolymers, etc. The microorganisms have an ability to reduce AuNPs due to the presence of enzymes, carbohydrates, proteins and biomembranes. Pourali et al. developed biosynthesis of AuNPs by two bacterial and fungal strains, *Bacillus cereus* and *Fusarium oxysporum* [30]. A number of enzymes are commercially available in pure form, which facilitates the purification and production of nanoparticles. Recently, Arib and co-workers described enzyme-assisted synthesis of hybrid polyedric AuNPs [31]. They applied manganese superoxyde dismutase (MnSOD), catalase (CAT) and bovine serum albumine (BSA) as the reducing agents in the presence of HEPES, known as Good's buffer. The MnSOD and CAT enzymes are known as oxydo-reductase (enzyme that catalyzes the transfer of electrons from one molecule) but with different catalytic activities.

In another study, da Silva and co-workers proposed a nanocomposite based on chitosan/AuNPs for the biomedical applications [32]. Chitosan, known as a biocompatible and biodegradable natural polymer, can reduce Au(III) and stabilize AuNPs and promote biocompatibility with composites, following approaches *in-situ*. It has a large number of reactive hydroxyl and amine groups that can be used for immobilization of biomolecules. For example, Majidi et al. developed antibody (Ab)-conjugated chitosan-AuNPs for optical biosensing systems [33].

Brust-Schiffrin method

The Brust-Schiffrin method discovered by Brust

and Schiffrin in 1994 [34], refers to the synthesis of thermally stable AuNPs with controlled size and uniform particle distribution. In Brust-Schiffrin approach, AuCl4- precursor was transferred from the aqueous solution to the toluene phase using tetraoctylammonium bromide carrier and was reduced by sodium borohydride in the presence of dodecanethiol [35]. The addition of the reducing agent caused the color of the organic phase to change from orange to dark brown, which indicated the formation of AuNPs.

Electrochemical method

The electrodeposition is one of the most controllable tecniques used for the preparation of nanoparticles, nanowires and nanoclusters of gold [36]. Electrochemical method was first studied by Reetz et al. in 1994 [37]. This method increases the quality and uniformity of the size distribution of nanoparticles [38]. It is superior to other methods of nanoparticle synthesis, due to lower processing temperature, high quality, low cost and ease of controlling the yield. An excellent control in size, shape and morphology has been reported by this method.

The production of AuNPs by electrochemical method is based on the electroreduction of auric ions on a rotating cathode in organic or aqueous solutions in the vicinity of a suitable stabilizer. The technological keys of this method lie in the choice of an ideal stabilizer and the use of a rotating cathode [39]. The rotating electrode prevents the deposition of gold film on the cathode and thus leads to the improvement of the efficiency in the formation of AuNPs in solution [34]. Electrochemical synthesis of AuNPs is often carried out in organic solvents, such as, tetra alky lammonium salts [40], cefazolin [41], polypyrrole [42], poly(N-vinyl-pyrrolidone) [38], poly(ethylen glicol) [37], antibiotics [43] and cationic surfactants [38] that behave as stabilizers. Despite many researches on the electrochemical synthesis of gold nanoparticles in organic solvents, there is little information about AuNPs produced by electrochemical methods in aqueous solution.

Sonochemical method

The sonochemical method is a simple and one-step procedure for the production of nanoparticles. Changing the parameters of the ultrasonic process leads to the control of the properties of the produced nanoparticles [44]. In addition, this process is a safe, environment-friendly, and economical technology.

Ultrasound irradiation can create conditions for the chemical agent-free reduction of Au(III) and production of AuNPs in different morphologies. Acoustic cavitation generated by ultrasonic radiation in water produces transient bubbles. The collapse of these bubbles plays an important role in the formation of AuNPs [45]. The high local temperature and pressure induced by implosion of transient bubbles causes sonolysis of water and formation of hydrogen and hydroxyl radicals. The formed free radicals lead to the promotion of the reaction and the formation of AuNPs [45].

Scientific literature has reported the effects of sonochemical parameters such as low radiation power (<100 W), frequency, reaction time and concentration of stabilizing compounds on the synthesis of AuNPs. For example, Dheyab and co-workers [46] observed that the particle size, stability, surface plasmon resonance and monodispersity of the AuNPs depended on ultrasound output power and reaction time. Okitsu et al. found that the size and distribution of the AuNPs produced in aqueous solutions containing 1-propanol was strongly dependent upon the ultrasound frequency [47].

Microwave irradiation method

Microwaves are an electromagnetic field that varies in time and space. Their frequency ranges from 300 MHz to 300 GHz. Microwaves can be used to enhance the synthesis of nanomaterials [48].

Microwave irradiation has higher reaction rate, faster volumetric heating, short reaction time, selectivity and high yield compared to conventional heating methods. It can produce nanoparticles with higher degree of crystallinity and a narrower size distribution. In addition, the size and shape of nanoparticles synthesized by this method are more controllable [49]. Gutiérrez-Wing et al. reported microwave-assisted production of AuNPs in the presence of 1-dodecanethiol with a mean diameter of 1.8 nm [50]. In another study, microwave-assisted synthesis of AuNPs and their antibacterial activity against *Escherichia coli* was reported by Arshi and co-workers [51]. In this research, the average particle size of AuNPs was ~4.05 nm for 40 s and ~1.05 nm for 70 s.

Gamma irradiation method

The gamma-irradiation-induced synthesis is

a clean and simple process without the use of excess reducers or the generation of undesirable oxidation products of the reductant. This method provides metal NPs in highly pure, fully reduced and highly stable state [52].

Gamma Co-60 ray irradiation (γ-Irradiation) is highly reactive with high reduction potential for the synthesis of AuNPs. It can lead to better control over distribution and size of AuNPs, due to its ability to precisely adjust radiation [53]. The γ-irradiation of aqueous solution generates transient radicals and solvated electrons through water radiolysis, which reduce the Au(III) ions eventually coalesce to form nanoparticles.

Microfluidic methods

Microfluidic appoaches are developed to manipulate the fluid flow in the microchips by significantly minimizing the volume of reagents. Efficiant and rapid mixing at ultra-low volumes make the microfluidic systems more suitable for prepration of nanoparticles with sizes, shapes, morphology and their unique properties. The microfluidic devices provide several benefits such as high reproducibility of synthesis, low reagent consumption, convenient control of experimental parameters, better mixing, reduced synthesis time and scale up potential. Despite these avantages, it has a compex design and sometimes requires special equipment such as cleanroom facilities [54].

Zhang et al. [55] developed an effective and simple microfluidic chip for the synthesis of AuNPs with precisely controlled sizes. The ultrafine and uniform AuNPs were produced by controlling the surfactant concentration, flow rate and temperature. Moreover, the AuNPs were fabricated continuously, and stably on a large scale with this system.

Top-down approach

Top-down synthesis is defined as the decomposition of bulk materials into smaller structures. Although this process facilitates the mass production of nanomaterials, it suffers from imperfect surface structures and crystallographic damage. These limitations strongly affect the physical and chemical properties of the surface of nanomaterials, and finally, if not well controlled, they also affect their intended applications [56].

Pulsed laser ablation

The pulsed laser ablation in liquid medium is a physical technique for the direct formation of AuNPs. The radiation absorbed by the target at the low laser flux resulted in the formation of an expanding plasma plume containing the ablated material. This method is the widely known as a versatile, competitive and green technique that allows the fabrication of capped or bare AuNPs with desired structural and physicochemical charateitics. The solvent type and different laser parameters, such as wavelength, pulse duration, fluence and repetition rate affect the surface chemistry, surface charge or size of nanoparticles. The great superiority of laser-produced AuNPs is the elimination of by-products or toxic substances due to the absence of chemical precursor and reducing agents [57]. For example, Gentile and co-workers prepared AuNPs by pulsed laser ablation in liquid whitout using the capping or reducing agent [58]. In another study, Mzwd et al. developed laser ablation synthesis of stable AuNPs in Gum Arabic solution [59].

Vacuume sputtering

Vacuum sputtering is based on applying a potential difference between two electrodes in a vacuum chamber filled with an inert gas such as argon. Argon gas is ionized under an electric field and then the metal target on the cathode is bombarded with argon plasma. As a result, the atomic clusters are punched out of the metal target and deposited on the electrode surface or dispersed into the liquid solution [60].

This method is a convenient and simple way to form metal NPs without chemical reactions. One of the most important features of AuNPs synthesized by vacuum sputtering is their purity [61]. No other chemical reactions or stabilizers are involved in this process.

Sputtering conditions play an important role in determining the nanoparticle size [62]. By carefully choosing the capture medium and the temperature, the size of the synthesized nanoparticles can be controlled. Hatakima et al. showed that the target temperature and applied voltages have a great effect on the size of AuNPs [62]. The higher applied voltage and lower target temperature are more suitable for production of smaller AuNPs.

Arc discharge

For the first time, the synthesis of AuNPs by DC arc discharge method in water without any surfactant or stabilizer using gold wire as electrode was proposed by Lung et al [63]. During

the arc discharge process, when the temperature between the electrodes reached several thousand degrees Celsius, the gold wires were etched in the water medium. Gold vapor condensed in water created a stable aqueous suspension. Well-separated nano-sized gold clusters in pure water were thermodynamically stable for a long time [64]. In fact, the high temperature generated as a result of the short circuit current led to the erosion of the bulk material of the electrodes and the formation of AuNPs [65]. Arc discharge in water is a fast, economic and environmentally friendly process for the production of AuNPs.

Role of surfactants in the synthesis of AuNPs

The stability of AuNPs is an important issue that determines their imminent use in nanobiotechnological applications. Most of the synthesized biomimetic nanoparticles are considered useless due to their instability in the aqueous environment [66]. Therefore, surfactants such as hexadecyltrimethylammonium bromide (CTAB) as a unique class of surface-active molecules are used to immobilize nanoparticles. Surfactants are used in the AuNPs fabrication when the reducing agent is not able to stabilize the NPs [67]. In addition, snthetic methods that enable precise control over nanoparticle morphology require shape (structure)-directing agents such as surfactants or polymers that force growth in a particular direction by adsorbing to specific crystal facets. So, surfactants can selectively block the growth of certain facets [68]. However, these reagents deactivate the surface of the nanoparticles, thereby reducing their performance in applications such as catalysis and surface-enhanced Raman scattering (SERS). Moreover, surfactants inhibit self-assembly reactions by preventing the binding of desired molecules, such as DNA and increasing the minimum achievable distance between constituent nanoparticles [68]. Therefore, the absence of surfactants and polymers makes the nanoparticle surfaces more accessible to molecules in solution thereby enhancing their performance in surface-area-dependent applications.

In general, surfactants have a significant ability to regulate the activity of NPs, provide specific functions, avoid their aggregation and create stable colloidal solutions. Surfactants also control the nucleation and growth processes of nanoparticles by modification of nuclei solubility and surface energy. The size of nanoparticles is influenced by the type of functional group (hydroxyl, thiol, carbonyl, carboxyl, amino and etc), length of its carbon chain and ratio of nanoparticle to surfactant [69].

Comparision of different synthesis methods based on various morphologies of AuNPs

Au nanomaterials can be synthesized in different forms, including nanoparticles, nanorods, nanoflowers, etc. Morphology as a fundamental property for nanostructured materials can have a significant impact on their applications. Table 1 contains a summary of some common Au nanomaterials based on different morphologies, along with information on synthesis methods [70-76].

Biological applications and proven capabilities of AuNPs

AuNPs are one of the most important

Table 1. Gold nanomaterials and their synthesis

Au nanomaterials	Methods	Precursor	Reducing agent	Capping agent (Stabilizer)	Ref.
Spherical Au nanoparticles	Chemical	Chloroauric acid	Sodium citrate	-----	[70]
Au nanorods	Seed-mediated growth	Chloroauric acid	1- Sodium borohydride 2-Ascorbic acid	CTAB (as the capping and structure-directing agents)	[71]
Au nanowires	Electrochemical	Chloroauric acid	No reducing agent	4-mercaptobenzoic acid	[72]
Au nanoflowers	Green synthesis	Chloroauric acid	Aqueous seed extract of Syzygium cumini (L.) Skeels	Starch	[73]
Au nanostars	Seed-mediated growth	Chloroauric acid	Sodium borohydride	Sodium citrate, CTAB (as the shape-directing and capping agents)	[74]
Au nanocages	Seed-mediated growth	Chloroauric acid	Sodium citrate	PVP and HMT (as the shape-directing and capping agents)	[75]
Au nanocubes	Seed-mediated growth	Chloroauric acid	Sodium borohydride	CTAC and sodium bromide (as the shape-directing and capping agents)	[76]

CTAB: Hexadecyltrimethylammonium bromide; PVP: Poly(N-vinyl-2-pyrrolidone); HMT: Hexamethylenetetramine; CTAC: Cetyltrimethylammonium chloride

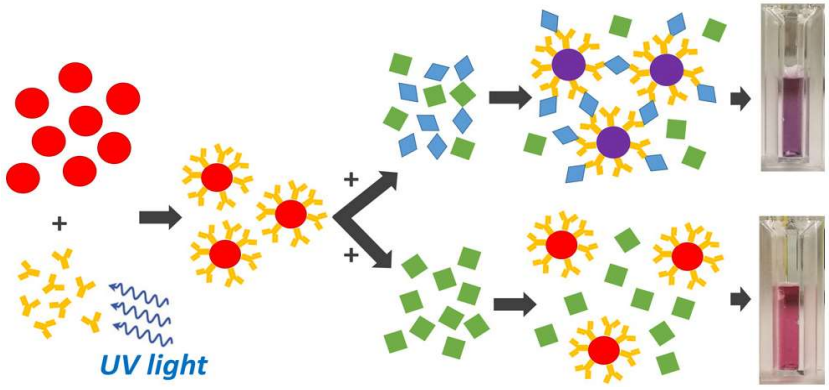

Fig. 3 Scheme of IgG detection based on AuNPs aggregation [78]; Reprinted by permission from ACS Publisher

nanoparticles that are widely used as ideal nanomaterials for medical and non-medical applications due to their outstanding characteristics, such as inertness, biocompatibility and especially low toxicity. They are versatile nanomaterials with a wide range of applications in a variety of fields, such as material sciences, chemistry, physics and medicine. In this section, we will summarize the most important applications of AuNPs in the biologcal field.

Biosensors/Sensors

Among the noble metal nanoparticles, AuNPs are the most used in the design of biosensors. The intelligent use of such nanoparticles led to a clear improvement in performance by increasing sensitivity and reducing detection limits by several orders of magnitude [77]. Here we will focus on the most common biosensors based on the AuNPs.

Colorimetric biosensors

The outstanding optical properties of AuNPs, including the color change depending on their size and shape, have led to the wide use of these nanoparticles in colorimetric biosensors.

Since the strong SPR absorption band of AuNPs in the visible region is affected by the shape, size or properties of the matrix surrounding the nanoparticles, the aggregation of AuNPs by the analyte leads to a significant bathochromic shift of the SPR band and a change in the color of the solution from red to blue. These color changes as a result of the aggregation of AuNPs can lead to species detection with the naked eye [77]. For example, Iarossi and co-workers designed a colorimetric immunosensor based on LSPR of AuNPs for the immunoglobin G (IgG) detection [78]. Because of the presence of multiple binding sites, IgG acts like linker and clustering takes place (Fig. 3). Zheng et al. reported a microfluidic colorimetric biosensor for rapid detection of *Escherichia coli* O157:H7 using the aggregation of AuNPs and smart phone imaging [79]. In another study, Mansouri et al. proposed a colotimertric biosensor based on the combination of the optical features of AuNPs and high affinity of aptamer for detection of tacrolimus [80]. Detetion of oxytetracycline in milk was also performed using a colorimetric biosensor based on the AuNPs and oxytetracline-short aptamer [81].

Electrochemical biosensors

The unique properties of AuNPs to create a suitable platform for stabilizing biomolecules while maintaining their biological activity and facilitating electron transfer have led to the intensive use of these nanoparticles for the construction of electrochemical biosensors with advanced analytical performance [82-84]. For example, Farzin and co-workers designed an electrochemical genosensor based on the format of DNA bioreceptor/gold-carbon dot (CD) core–shell NPs/graphite nanocrystals (GNC)/paper electrode for the determination of SARS-CoV-2 RdRP gene [85]. They observed that the peak current of Au@CD NPs/GNC/paper electrode compared to the GNC/paper electrode increased. This confirms that the deposition of Au@CD NPs on the modified electrode leads to the improvement of the electrical conductivity and thus to the increase of the electron transfer rate.

Fluorescence-based biosensors

Gold nanoparticles are known as outstanding fluorescence quenchers that are 9-10 times more efficient than conventional small molecule

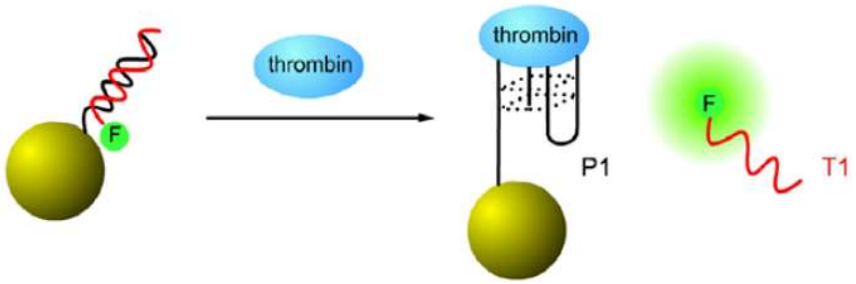

Fig. 4. Principles of thrombin detection with aptamer functionalized AuNPs [87]; Reprinted by permission from Elsevier Publisher

quenchers [86]. Based on this phenomenon, a large number of fluorescence biosensors based on the on/off strategy including fluorescent dyes and AuNPs have been designed. For example, Wang et al. designed a fluorescence-based biosensor using the combination of AuNPs as fluorescence quencher and aptamer as bioreceptor [87]. In this study, AuNPs was functionalized with the thiolated anti-thrombin aptamer (P1), and then dye-labeled complementary DNA (T1) hybridized with P1, so that the fluorescence was quenched. Upon introduction of thrombin, binding of the target with P1 caused dissociation of the duplex and release of dye-labeled T1 from AuNP surfaces, and the fluorescence signal recovered sequentially (Fig. 4).

Drug delivery

In most of the cancer treatment protocols, the first-generation chemotherapy agents are used. Chemotherapy can shrink tumor or slow down its growth. Despite the fact that chemotherapy leads to an increase in the patient's life, its side effects and drug resistance are very worring.

AuNPs are known as the ideal tools for targeted and selective drug delivery due to their remarkable size and surface characteristics. They can be easily engineered to deliver the drug directly to the tumor site. The various types of ligands, such as aptamers, peptides, proteins, small molecules and etc can be loaded on the surface of AuNPs to modulate drug release or increase selectivity [88]. For example, Go et al. proposed PrPC aptamer conjugated-AuNPs for targeted delivery of doxorubicin to colorectal cancer cells (CRC) [89]. They demonstrated that the PrPC aptamer conjugated-AuNPs decreased proliferation and increased apoptosis of CRC cells to a greater degree. Bayat and co-workers synthesized aptamer AS1411-functionalized AuNPs-melittin complex [90]. They observed that as-produced complex had a potential value in the targeted delivery of melittin to the MCF-7 cell line in breast cancer. In another research, Kudirat et al. introduced AuNPs conjugated with polyethylene glycol (PEG) loaded with chloroquine diphosphate as an improved antimalarial drug [91].

Photothermal therapy

Photothermal therapy has been recognized as a minimally invasive method for the treatment of cancer. In this method, the photon energy converted into heat leads to the killing of cancer cells. The plasmonic AuNPs as the attractive photothermal agents for cancer therapy show efficient local heating upon excitation of surface plasmon oscillations [92]. The intrinsic low toxicity, strong absorption, efficient heat conversion, high light stability and distinct surface chemistry of AuNPs lead to increased interest in their photothermal therapeutic applications [93]. Despite these advantages, long retention and shape-dependent photothermal effects of AuNPs as well as the high cost have limited their further applications [92]. The absorption of spherical AuNPs is weak in the near-infrared (NIR) window, where light has its maximum depth of penetration in tissue. So, the spherical AuNPs have a low photothermal efficiency within this window [94]. Among the various shapes of AuNPs, gold nanostars show the highest photothermal conversion efficiency [95].

Wang and co-workers showed that fibrous nanostructures assembled from spherical AuNPs can improve the photothermal efficiency in the NIR window because the templating effect of silk fibroin (SF) can shift the optical absorption to the NIR [94]. In this study, *in vitro* and *in vivo* analyses proved that AuNPs/SF nanofibers could efficiently kill breast cancer cells and destruct breast cancer tumor tissues under one-time NIR irradiation for 6 min by photothermal therapy but nonassembled AuNPs could not (Fig. 5).

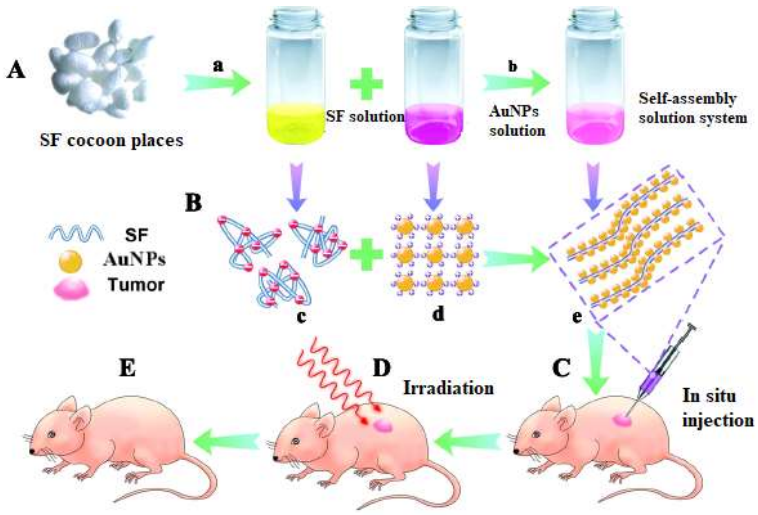

Fig. 5. Schematic diagram of the templated assembly of AuNPs on SF fibers into AuNPs/SF nanofibers and their use in photothermal breast tumor destruction [94]; Reprinted by permission from ACS Publisher

Theranostic radiopharmacy

The theranostics radiopharmaceuticals (Radiotheranostics) are used for both therapeutic and diagnostic purposes by targeting one specific tumor receptor. The use of AuNPs in the development of theranostics radiopharmaceuticals has provided different nanosized platforms for the delivery of medical radioisotopes for nuclear imaging and radionuclide therapy [96]. For example, the peptide-functionalized 198AuNPs were proposed for the targeted cancer therapy [97]. *In vitro* studies showed specificity of peptide-functionalized 198AuNPs towards melanoma cell line. Administration of peptide-functionalized 198AuNPs led to considerable regression of tumor growth with no apparent body weight loss over a period of 15 d.

AuNPs were widely used to be doped or labeled with various radionuclides, such as 99mTc, 125I, 131I, 198Au and 111In for single photon emission computed tomography (SPECT) imaging of tumor owing to their unique physical/chemical properties, high surface area and controlable morphologies [96]. For example, Li and co-workers have synthesized multifunctional dendrimer-gold nanocomposites, which are labeled with 99mTc and functionalized with folic acid for the SPECT imaging of tumors [98]. In addition, positron-emitting radionuclides-decorated AuNPs can be utilized for the positron emission tomography (PET) imaging. Pretze et al. evaluated targeted 64Cu-labeled AuNPs for PET imaging [99].

Despite these advances, radiolabeled gold-based nanomaterials are currently not use in the clinic. In order to develop the biomedical application of radionuclide labeled/doped gold-based nanomaterials in the clinic, the more intensive and longer biosafety studies should be performed in the clinical trial. Moreover, these AuNP-based radioprobes should be able to be excreted from the body of mice within a few hours without side effects [100].

Nanobrachytherapy

Brachytherapy (low dose-rate radiation and high dose-rate radiation) is generally applied for the solid tumor treatment. For example, permanent placement of radioactive seeds in the prostate gland results in the delivery of low doses of radiation over several months. Despite much research in this field, the successful implementation of this technique is hampered by several adverse post-treatment effects or symptoms and associated operative complications. Recently, with the development of nanotechnology, tumor specific biomolecules-functionlized radioactive nanoparticles have been proposed as an alternative to seed-based brachytherapy. For example, Axiak-Bechtel et al. reported brachytherapy with high dose-rate radiation using gum arabic (GA)-coated 198AuNPs for treatment of prostate cancer [101]. The GA-coated 198AuNPs have several advantages compared to the traditional brachytherapy, such as higher dose-rate irradiation and homogenous dose distribution.

Radiation dose-enhancement

Radiotherapy (RT) is an effective method for cancer treatment, but often results in collateral damage to nearby healthy tissues. To increase the treatment efficiency without damaging the nearby tissue, radiosensitization has been shown to be essential. The high-atomic-number materials, such as AuNPs, are known to sensitize cancer cells to radiation therapy by increasing the deposition of ionizing energy in their immediate vicinity [102-105]. AuNPs promot cancer radiotherapy efficiency by fousing the absorption of radiation energy in the tumor while protecting surrounding normal tissue from radiation toxicity. Monte Carlo simulation of microdosimetry has indicated that the increase in dose near the surface of AuNPs is the highest and decreases with increasing distance [106]. Bemidinezhad et al. observed that the glucose-coated AuNPs can increase the radiosensitivity and lead to the death of U87 glioblastoma cells at the optimal concentration [107].

Immunotherapy

Malignant tumor immunotherapy as a new approved antitumor strategy leads to increased survival of cancer patients. This tactic activates the immune system to recognize and damage cancer cells, thereby preventing their proliferation. However, immunotherapy still faces many challenges in terms of clinical efficacy and safety issues [108]. Various nanomaterials, especially AuNPs have been proposed as the immune agents to enhance cancer immunotherapy. AuNPs can not only act as immunomodulators, but also deliver immune drugs for cancer. Therefore, these nanoparticles are considered as candidates for increasing the efficiency and safety of cancer immunotherapy [108]. Zhang et al. for the first time, produced immunological AuNPs inside the cell and applied these nanoparticles for combined immunotherapy and photothermal against tumor [109]. In another attempt, Javanmardghooghan and co-workers proposed AuNP-based sublingual immunotherapyin the asthmatic mice [110]. Lee et al. developed dendritic cell-based cancer immunotherapy and also dendritic cell imaging with PET and Cerenkov luminescence using the radionuclide-embedded AuNPs [111]. For this purpose, they investigated the anti-tumor immune responses induced by the redionuclide-AuNP-labeled dendritic cells in mice model with murine lung cancer cell lines. The enhanced antitumor immunity is believed to originate from the stimulated immune response of dendritic cells mediated by AuNPs.

CT imaging

CT scan or computed tomography is one of the diagnostic imaging methods that uses a combination of X-rays and computer technology to produce high-resolution three-dimensional images of the inside of the body. The contrast between tissues in the CT image is created by the difference between X-ray attenuation. Since the attenuation of X-rays has little difference for soft tissues, it leads to difficulty in detecting the surrounding tissues. The contrast materials based on the iodine can overcome these limitations.

Despite the widespread use of iodine, there have recently been many reports of AuNPs-based contrast agents for CT imaging. AuNPs have outstanding features for this application such as good biocompatibility, tunable shapes and sizes, high volumes of contrast material, strong X-ray attenuation and appropriate surface chemistry [112]. They possess better X-ray attenuation property than other conventional iodine-based computed tomography (CT) contrast agents. At 80 Kilovoltage peak (80 kVp), AuNPs provide 3.03 times more contrast than iodine at a concentration of 5000 μM [113]. Oumano et al. reported CT imaging of AuNPs in a human-sized phantom [114]. They showed that AuNPs result in optimal image contrast at 120 kVp in a human-sized phantom due to gold's 80.7 keV k-edge and the attenuation of x-rays by tissue. Typical CT contrast agents, like iodine, require the use of lower kVps for optimal visualization, but lower kVps are more difficult to implement in the clinic because of elevated noise levels, elongated scan times, and/or beam-hardening artifacts. This represents another great advantage of AuNPs over iodine not yet discussed in the literature. In another study, Hainfeld and co-wokers showd that Micro-CT can enable quantification within various regions of a tumour [115]. AuNPs are largely confined to the tumor environment, and even without antibodies, they provide useful CT contrast that allows the detection of small millimeter-sized tumors. When AuNPs are attached to tumor-specific antibodies, they provide additional specific radiocontrast. Sun et al. synthesized heparin-coated AuNPs (HEPA-AuNPs) with prolonged stability, low toxicity and an enhanced X-ray absorption coefficient [116].

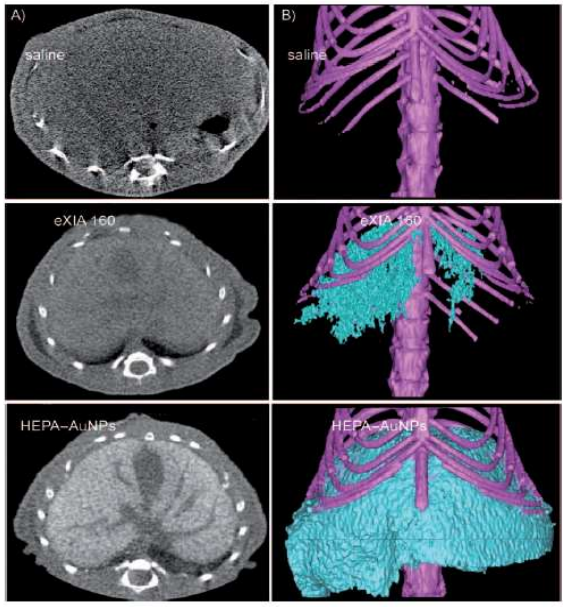

Fig. 6. A) Cross-sectional microCT images in livers 2 h post injection of saline, eXIA 160 and HEPA–AuNPs; B) Three-dimensional microCT images of livers obtained after 2 h post injection of saline, eXIA 160 and HEPA–AuNPs [116].

Their achievements showed that HEPA-AuNPs can enhance contrast of liver-specific CT images compared with iodine-based contrast agents, such as eXIA 160 (Fig. 6).

MRI

Magnetic resonance imaging (MRI) using a powerful magnetic field is recognized as one of the most widely powerful tools for non-invasive clinical diagnosis. It can produce three dimensional (3-D) detailed anatomical images due to its high degree of spatial resolution, soft tissue contrast and depth of penetration. To increase contrast, magnetic NPs and various mineral complexes are used before scanning. These contrast agents lead to the MRI signal intensity by selectively reducing the relaxation time of water protons [117].

Currently, the most commonly used compounds for contrast enhancement are gadolinium-based chelates. They have serious disadvantages such as high dose associated-nephrotoxicity and low longitudinal relaxivity value that restrict their wide applications [118]. In addition, the safety of gadolinium-based contrast agents used in MRA is one of the biggest concerns in recent years. These emphasize the need for biocompatible and stable compounds with high contrast. Magnetic NPs such as iron oxide NPs are the best choice for MRI, due to biocompatibility, exceptional chemical stability, targeting ability, biological degradability and magnetic qualities [119]. Unlike paramagnetic gadolinium (Gd) based-chelates, iron oxide NPs are supermagnetic contrast agents [119].

In recent decades, core-shell magnetic NPs have been intensively investigated in the field of imaging. The integration of several nanoparticles creates new opportunities to improve a variety of emerging applications of hybrid nanomaterials. They are able to combine the properties of at least two different nanomaterial. For example, Fe3O4@Au NPs have gained substantial attention because of their capabilities as a multifunctional contrast for CT and MRI imaging [120]. They showed good stability in aqueous environments and the ability to convert light into usable heat in the near-infrared region. In another study, the folic acid-functionalized Fe3O4@Au nanostars were developed for the photothermal therapy of tumors and targeted multi-mode MR/CT imaging [121]. Li and co-workers reported the use of hyaluronic acid-functionalized Fe_3O_4@Au nanostars for MR/CT imaging and photothermal therapy of tumors [122]. Further sequential modification of nanostars with polyethyleneimine results in targeting specificity for CD44 receptor overexpressing cancer cells and good biocompatibility.

Antimicrobial activities

Currently, despite the great progress in obtaining effective antimicrobial agents, research on new microbicidal nanomaterials with the ability to limit biofilm formation, demonstrate satisfactory biocompatibility and eradicate pathogens is necessary. Silver nanoparticles (AgNPs) are particularly well known for their high efficiency in killing a wide range of bacterial pathogens, including Escherichia coli or Staphylococcus aureus [123]. Although the results of laboratory studies have shown that the AgNPs have adverse health effects in the mammalians [124, 125]. The development of AgNPs-based drugs can be led to the direct entry of these nanoparticles into the human circulatory system. Some researches also point to the use of AuNPs that target bacteria and fungi. Although the DNA and plasma membrane of bacteria are the main targets of AuNPs, other molecules such as components of pseudo-apoptotic pathways have been proposed as targets. The size, shape and surface functional groups of AuNPs affect their interaction with bacterial cells and their subsequent entry into the cytoplasm

Table 2. A summary of the applications of AuNPs based on their inherent properties

Application	Inherent characteristics
Colorimetric sensing	Surface plasmon resonance
Electrochemical sensing	Electrical conductivity, Electrocatalysis
Fluorescence-based sensing	Fluorescence quenching
Drug delivery	Loading of various types of ligands, such as aptamers, peptides, proteins, small molecules and etc on the surface of AuNPs
Photothermal therapy	Strong light absorption, High photothermal conversion efficiency
Theranostic radiopharmacy	Ability to be doped or labeled with various radionuclides, Characteristic gamma or beta emission from ^{198}Au
Nanobrachytherapy	Homogenous dose distribution, Higher dose-rate irradiation
Radiation dose-enhancement	Focusing the absorption of radiation energy in the tumor
Immunotherapy	Immunomodulating, Delivery of immune drugs to cancer cells
CT imaging	Strong X-ray attenuation
MRI	Ability of core-shell magnetic AuNPs to increase contrast
Antimicrobial activities	Ability to kill a wide range of bacteria and fungi

CT: Computed tomography; MRI: Magnetic resonance imaging

of pathogens. Controlling these features leads to improving the bactericidal efficiency of AuNPs [126]. Mishra et al. showed antimicrobial activities of AuNPs produced by Trichoderma viride and Hypocrea lixii [20]. In another study, Zhang and co-workrs reported that AuNPs are antifungal [127].

Smmary of biological applications of AuNPs

AuNPs have tunable optical and electronic properties and can be used in a number of biological applications. Table 2 shows a summary of the applications of AuNPs based on their inherent properties.

CONCLUSION

The past decade has witnessed the huge development of AuNPs and their applications in diverse biological domains, a field in which nanoparticles show great potential. A lot of research has been done to improve the production methods of AuNPs. The aim of these studies is to achieve more stable AuNPs with the desired shape and size and less toxicity to reach the target tissue. Due to special optical and electrochemical properties, synthetic versatility, excellent X-ray attenuation ability, high X-ray absorption, simple surface modification, photothermal properties and good biocompatibility, these nanoparticles can be used for bioassay strategies, cancer treatment, drug delivery, enhanced radiotherapy, nanobrachytherapy and also used as CT contrast agents. The previous studies have shown that AuNPs increase the efficiency of cancer radiotherapy by focusing the absorption of radiation energy in the tumor, while reducing radiation toxicity to surrounding normal tissues. In addition, a number of studies have described the antimicrobial properties of these nanoparticles. Considering the importance of AuNPs, in this minireview, the production methods and applications of AuNPs have been summerized with an emphasis on their green synthesis. Applications of AuNPs in bioassays, imaging and treatment of cancer have also been noted, which shows their potential in the clinic.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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