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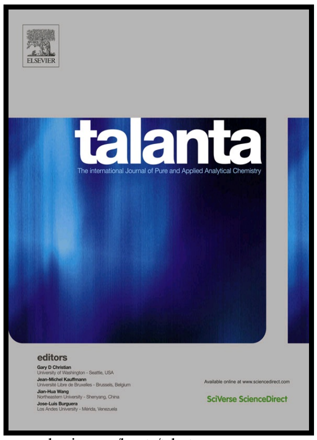

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Recent biomedical applications of gold nanoparticles: A review

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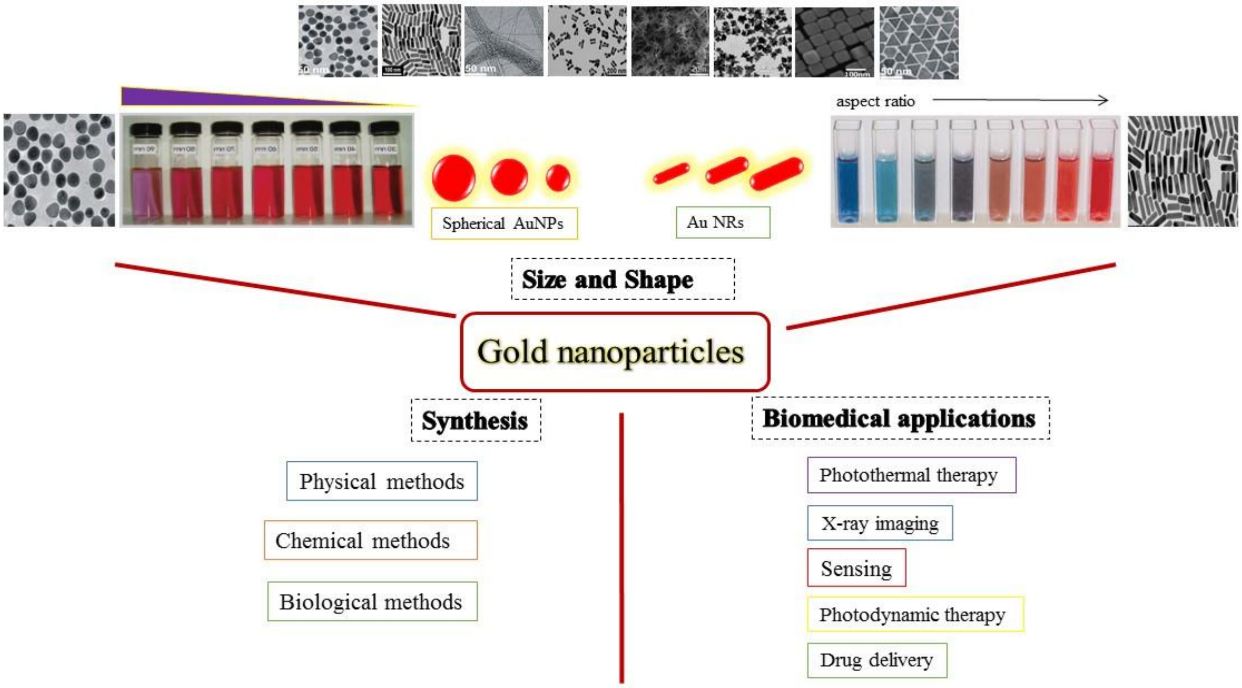
ABSTRACT

Recent advances in nanotechnology are as a result of the development of engineered nanoparticles. Efficiently, metallic nanoparticles have been widely exploited for biomedical application and among them, gold nanoparticles (AuNPs) are highly remarkable. Consequent upon their significant nature, spherical and gold nanorods (Au NRs) nanoparticles attract extreme attention. Their intrinsic features such as optical, electronic, physicochemical and, surface plasmon resonance (SPR); which can be altered by changing the characterizations of particles such as shape, size, aspect ratio, or environment; ease of synthesis and functionalization properties have resulted to various applications in different fields of biomedicine such as sensing, targeted drug delivery, imaging, photothermal and photodynamic therapy as well as the modulation of two or three applications. This article reviewed the popular AuNPs synthesis methods and mentioned their established applications in various demands, especially in biological sensing.

Graphical abstract



Keywords: Gold nanoparticles, gold nanorods, properties, synthesis, biomedical applications, biosensor.

1. Introduction

Recent studies have shown the significant roles of nanomaterials in the progress of nanoscience and nanotechnology [1, 2]. In comparison to either small molecules or bulk materials, nanoscale structures express various physical and chemical properties. Nanoparticles possess particular intrinsic reactivity as a result of increased surface area, so an appropriate choice of materials for the manufacture of nanoparticle-based therapeutics would be made. The surface functionalities and depending on the particle size, shape and state of aggregation, the interaction will occur between nanomaterials and biological systems in various ways depending on the cell type, employing different uptake routes or targeting different organelles [3]. Among the different types of nanomaterials, metal nanoparticles especially AuNPs have attracted tremendous interests [4] from different fields of science, due to their particular features: high X-ray absorption coefficient, ease of synthetic manipulation, enabling precise control over the particle's physicochemical properties [5], strong binding affinity to thiols, disulfides and amines [1], unique tunable optical [6] and distinct electronic properties [4]. Since the early twentieth century, various investigations have been conducted on the existence of anisotropic AuNPs. The structural, optical, electronic, magnetic, and catalytic properties of anisotropic AuNPs are different from, and most often superior to spherical gold nanoparticles [7].

Based on dimensions, AuNPs can be divided into three parts: a) one-dimensional AuNPs: nanorods, nanowires, nanotubes, nanobelts b) two dimensional AuNPs: gold nanoplates such as stars, pentagons, squares/rectangles, dimpled nanoplates, hexagons, truncated triangles and, c) three dimensional AuNPs: gold nanotadpoles, gold nanodumbbells (AuNDs), branched AuNPs such as nanopods, nanostars and gold nanodendrites. The anisotropy of these nonspherical, hollow, and nanoshell AuNP structures is the source of plasmon absorption in the visible region as well as in the near infrared (NIR) region, which is especially sensitive to the AuNP shape. This property has given rise to medical applications such as diagnostics and therapy [8]. Spherical or quasi-spherical gold nanoparticles have received the most attention because of the ease of synthesizing such structures [9]. Besides, Au NRs as a kind of elongated AuNPs, have attracted a great deal of scientific interest due to their anisotropic shape, display two separate SPR bands, as well as transverse (TSPR) and longitudinal plasmon bands (LSPR) [9]. The transversal band and the longitudinal band occur in the visible region and in the near infrared region (NIR) respectively [10]. The absorption in the NIR region produces maximal penetration of light in tissues. This makes the Au NRs suitable for *in vivo* applications. In addition, the converting of luminous energy into heat by localized SPR of Au NRs makes them an appropriate candidate for photothermal therapy [10]. Unique intrinsic features of these type of metals nanoparticles are fundamental to major biomedical applications. Optical, electronic, physicochemical properties and ease of synthesis of Au NRs provide an appropriate situation for nanotechnology improvement. Particularly, optical properties of Au NRs are tunable with their shape, leading to sensing, imaging, and biomedical therapeutic applications [11].

2. Properties of AuNPs

Explicit physical and chemical attributes make AuNPs prodigious scaffolds for various applications in therapeutics, detection and diagnostics, biolabeling, drug delivery [6, 12], chemical and biological sensing, imaging [13], nonlinear optics, photovoltaics, and catalysis fields [4, 14]. The dominant features of AuNPs include shape-related optoelectronic properties, large surface-to-volume ratio, excellent biocompatibility and low toxicity, these properties make them outstanding tools in biotechnology [15]. The surface plasmon resonance (SPR) band of AuNPs, as well as their important physical properties [15, 16], depend on their morphology (shape, solvent, surface ligand, core charge, temperature) and physiology [15, 17].

The intrinsic optical properties of AuNPs provide the opportunity of being composite therapeutic agents in the clinic. The morphology and physiology of AuNPs is associated with optical features. Changing the size of the nanoparticles, affects the color of colloidal AuNPs. This trait utilizes the fundamental of colorimetric detection forms [18]. In aqueous solution, spherical AuNPs demonstrate (present) a range of colors (orange, red to purple) as there is growth of core size from 1 to 100 nm with the exhibition of size relative absorption peak from 500 to 550 nm [15].

In recent times, researchers have focused on developing methods for the synthesis of different controllable particles shapes and sizes (Fig. 1). As the pictures indicate, a variety of morphologies and sizes of the nanoparticles have specific optical property. It may turn in both the visible and near-infrared spectrum (Fig. 2.) [19].

3. Synthesis of AuNPs

To date, there are numerous preparative methods for the synthesis of AuNPs, containing top-down and bottom-up procedures (Fig. 3.). Recent efforts have been dedicated to controllable approaches involving size, shape, solubility, stability, and functionality [15].

Generally, procedures for the synthesis of Au NPs can be arranged into chemical, physical and biological methods.

(i) Methods such as the γ-irradiation method, microwave (MW) irradiation, sonochemical method, ultraviolet (UV) radiation, laser ablation, thermolytic process and photochemical process are categorized as physical procedures [17]. The γ-irradiation method renders controllable size and high purity of nanoparticles with a diameter of 5 - 40 nm. In the microwave irradiation method, heating or photochemical reduction method was utilized to form Au NPs [27]. The sonochemical method is capable of providing Au/Pd bimetallic particles and AuNPs within the pores of silica [28]. High temperature and ultraviolet (UV) radiation are the main reducing agents in thermolytic and ultraviolet (UV) radiation methods of AuNPs synthesis. By optimizing the synthesis condition, various sizes were achieved [29]. Photochemical process provides Au NRs. These one-dimensional nanoparticles possess extremely complex physical properties and self-assembly behaviors compared to those of spherical nanoparticles [30]. The laser ablation method can be used to produce AuNPs with tunable features. The reduction of gold (III) tetrachloroaurate is performed by the photo-induced effects of a 532 nm wavelength laser beam.

(ii) In chemical methods, chemical reactions are performed in an aqueous medium by a reduction agent. Citrate and sodium borohydride are the common reducing agents used. Among the conventional methods of chemical synthesis of colloidal gold, the Turkevitch procedure is highly utilized due to the simplicity and ease of synthesis, controllable size, and stability of colloidal nanoparticles [31]. In 1951, Hauser and Lynn ‘s preparation was modified by Turkevich. In the standardized procedure, sodium citrate reduced and stabilized the solution. It provides spherical AuNPs with a narrow size distribution [32]. The Brust−Schiffrin method expressed in 1994, utilized potent thiol−gold interactions to protect AuNPs with thiol ligands [14]. In the presence of alkanethiols, $AuC1_4^-$ was reduced by sodium borohydride. This reaction was performed in two-phases (water-toluene) and nanoparticles with diameters in the range 1-3 nm were produced [33].

(iii) Biological synthesis known as favorable environment is another route of synthesis [34]. Reducing hazardous generated wastes and assisting “green chemistry” are the main objectives of biosynthesis. Solvent medium, reducing and stabilizer agents should be nontoxic and safe [35]. Plant-based compounds and derivatives, bacteria, fungi, algae, yeast, and viruses are employed as the common resources [31, 35-37]. As shown in Table 1, various shapes and sizes of nanoparticles would be obtained from these resources which have many effective applications in biomedical sciences.

4. Applications of AuNPs

4.1. Photodynamic therapy

Photodynamic therapy (PDT) is regarded as an important treatment for oncological diseases and certain skin or infectious diseases employ photosensitizers as light-sensitizing agents and a laser (the wavelength associated with a peak of dye absorption). Apoptosis or necrosis is induced in tumor cells by singlet oxygen and highly active free radicals generated via the energy of photosensitizers [79, 80].
Effective fluorescence quenching and surface plasmon resonance (SPR) absorption are the significant features of AuNPs which have been utilized in photodynamic therapy. Besides, gold conjugation facilitates intracellular penetration, due to its tendency to bind with thiols, disulfides, and amines [79].

4.2. Photothermal therapy

Photothermal therapy (PTT) known as thermal ablation [80] or optical hyperthermia [81] is a highly applied method in cancer therapy with minimal invasiveness [82-84] and it has attracted a great deal of attention in recent years [85]. AuNPs with maximum absorption in the visible or near IR region, receive light and generate heat. The heat causes the death of malignant tumors [79, 84]. Spherical solid AuNPs, with a diameter larger than 50 nm due to strong near-infrared (NIR) absorption is more common in PTT [82]. Figure 4 shows the schematic application of AuNPs in PTT and it was suggested to call this method plasmonic photothermal therapy (PPTT). Furthermore, AuNPs–antibody conjugates can be applied for both diagnosis and PPTT; the methods of what is known as theranostics. Like the PDT, binding properties of AuNPs play a key role in the process of intracellular transfer [79].

4.3. X-ray imaging

AuNPs have attracted the main attention as an x-ray contrast agent because it represents a high X-ray absorption coefficient, ease of synthetic manipulation, nontoxicity, surface functionalization for colloidal stability and targeted delivery. Common vascular contrast agents such as iodinated molecules have low-molecular weight. The water solubility of these iodinated aromatics are high and are indicative of low toxicity. Nevertheless, the blood circulation time is short and is rapidly eliminated through the kidneys. Hence, a short imaging window may require multiple injections with the risk of developing thyroid dysfunction. Au NPs have dominated the challenges [86]. The development of an imaging window due to longer vascular retention time compared with common agents is the consequence of significant properties of AuNPs [13, 86].

4.4. Drug delivery

As earlier described, considerable features of AuNPs such as unique optical, physicochemical properties, biocompatibility, functional flexibility, tunable monolayers, controlled dispersity, high surface area for loading the density of drugs, stability and nontoxicity make them an efficient nanocarrier in drug delivery systems (DDSs) [27, 31, 87]. These effective nanocarriers

are capable of transferring various drugs such as peptides [88], proteins [89, 90], plasmid DNAs (pDNAs), small interfering RNAs (siRNAs), and chemotherapeutic agents [91].
Besides the spherical nanoparticles, recent researchers have proposed stable colloidal gold nanorods as an appropriate agent for drug delivery. PEGylated Au NRs have provided a sufficient drug transfer by avoiding the reticular-endothelial system (RES) clearance. The other candidates are gold nanocages. By binding the cancer cell receptors to the nanocages surface conjugated with bioactive molecules such as antibodies, targeted drug delivery takes place. Verigene (FDA-approved) and Aurimmune (Phase-II) are gold based nanomaterials for the application of therapeutics [92].

4.5. Sensing

One of the major applications of AuNPs is in chemical and biological sensing. Utilizing the intrinsic features, Au NPs have been used as efficient sensors for the detection of different analytes such as metal ions, anions, and molecules like, saccharides, nucleotides [4], proteins [16, 93] and toxins [94]. Figure 5 shows various nanobiosensors based on AuNPs features. Regarding the intended detection and various properties of AuNPs, the sensor has been constructed. According to the sensing strategy, the AuNPs sensors can be colorimetric, fluorescence-based, electrical and electrochemical, surface plasmon resonance, surface enhanced Raman scattering (SERS)-based, quartz crystal microbalance-based and Bio-Barcode assay sensors [14]. Different types of nano-biosensors have employed special features of AuNPs.
The fundamentals of colorimetric sensing is based on visible color change due to the aggregation of AuNPs, fluorescence-based sensors: the fluorescence quenching feature of AuNPs, electrical and electrochemical sensors conductivity, high surface area and catalytic properties of AuNPs, Au NP-based surface plasmon resonance sensors: the optical properties (surface plasmon resonance, SPR) of AuNPs [16], surface-enhanced Raman scattering (SERS)-based sensors: the inelastic scattering of photons by AuNPs due to quantized vibrational level/signature, Au NPs in Quartz Crystal Microbalance-Based Sensing: the high surface area of AuNPs for enhancing detection sensitivity and Au NP-Based Bio-Barcode Assay: strong binding affinity of AuNPs to thiols and visible color change due to aggregation of AuNPs [14, 15, 95].

Among the different types of AuNPs, gold nanorods attract much attention for biosensing due to their substantial and unique optical properties. Optical absorbance and its changes are the main markers for the construction of sensitive biosensors [9].

5. Gold nanorods

Gold nanorods, as a kind of elongated AuNPs, and due to their anisotropic shape [9], possess two plasmon resonance absorptions in the visible and NIR regions, respectively, produced by transverse (TSPR), short axis, and longitudinal (LSPR), long axis, oscillation of electrons, but the spherical-shaped AuNPs have one absorption band in the visible region [10, 96, 97]. The absorption wavelength of the longitudinal bands is impressed by the aspect ratio of the nanorods and different colors are observed [10, 96]. The uptake, removal, and toxicity of Au NRs is associated with physiochemical properties such as surface groups and modifications, charge, size, shape and aspect ratio [98]. These attractable optical and unique physiochemical properties play a key role in various biomedical applications of Au NRs such as photothermal therapy, and near-infrared imaging, X-ray computed tomography, photoacoustic imaging, biosensing, drug/gene delivery, and thermal therapy of tumor [10, 96].

5.1. Synthesis of Au NRs

Well-defined size and shape synthesis of Au NRs has been considered in recent years due to the optical, electronic, physicochemical features of these nanomaterials. Various methods have been proposed for the production of Au NRs (Table 2). The first Au NRs were synthesized by the electrochemical method in 1997. Gold as the anode and platinum as the cathode were plunged in an electrolytic solution containing the cationic surfactant, hexadecyltrimethylammonium bromide (CTAB), and a cosurfactant. AuNPs were formed by turning the balk gold metal (the anode form) into nanoparticles [10, 99].

The seeded growth synthesis of Au NRs is known as a convenient and versatile method and had been conducted between 1999 and 2004 [100]. Since then, various modifications have been performed on seeded growth syntheses [100-105], and it still has its own enthusiasts [102, 103]. Briefly, by adding the spherical 'seed' nanoparticles (~4 nm) to a growth solution such as gold salt, silver nitrate, ascorbic acid, and cetyltrimethylammonium bromide (CTAB), the rod like particles are formed [97].

5.2. Applications of Au NRs

Tunable surface plasmon and photothermal effects [106], the broadly accepted biocompatibility and functional versatility [107] of Au NRs are the basis of a wide range of biomedical sensing (Table 3), drug delivery [107-109], thermo-chemotherapeutic [106] and, PTT [106, 110-113] applications. Besides, these potential features, and its unparalleled nature establish promising multipurpose applications. The utilization of Au NRs as a suitable carrier, benefits their surface plasmon resonance for converting the incident light energy (NIR) into heat energy, is the foundation of major targeted drug delivery applications which combined with photothermal ablation for cancer therapy. Some multi-function applications of Au NRs include targeted cancer imaging and PTT [114, 115], cell imaging and drug delivery [116], therapeutic and imaging applications [117], drug delivery and therapeutic applications [118], drug delivery and PTT [96, 119-125], imaging and PTT [126-128], PDT and imaging [129-131], Near-Infrared Fluorescence imaging and photodynamic/photothermal therapy application [132], and PDT [133-138]. These are some multi-function application of Au NRs.

Biosensors have made a tremendous transformation in the detection of various substances especially medical diagnosis. In the meantime, AuNPs particularly Au NRs play a key role in the design of different types of nanobiosensors due to their inherent properties. Based on the transducer, piezoelectrical, optical, electrochemical and thermal/ calorimetric biosensors are designed. Among different AuNPs structures, Au NRs are appropriate candidates. The high surface area with efficient mass transport characteristics and eligible biocompatibility [139], extreme sensitive longitudinal SPR [140-142], high stability under high ionic strength conditions without addition of any stabilizing agent [143] are some significant features of Au NRs for progression of sensitive and selective biosensors.

6. Conclusions

In recent years, the conventional biomedical methods have been successfully replaced with modern nanotechnology methods for considerable accuracy, much sensitivity, efficiency and high-speed measurement. Among the various applied types of metallic nanomaterials, AuNPs have attracted particular attention as a result of their intrinsic features. Obviously, there has been a great promotion in the synthesis, functionalization of AuNPs, which has resulted in advanced diagnostic and therapeutic procedure. Spherical and nanorods have been devoted a special place by optical, electronic, physicochemical, surface plasmon resonance (SPR) properties. Au NRs have been a suitable candidate for localized surface plasmon resonance technique. Besides, utilizing the different properties, plentiful technique assays can be designed and multipurpose applications have been attained which require more investigations.

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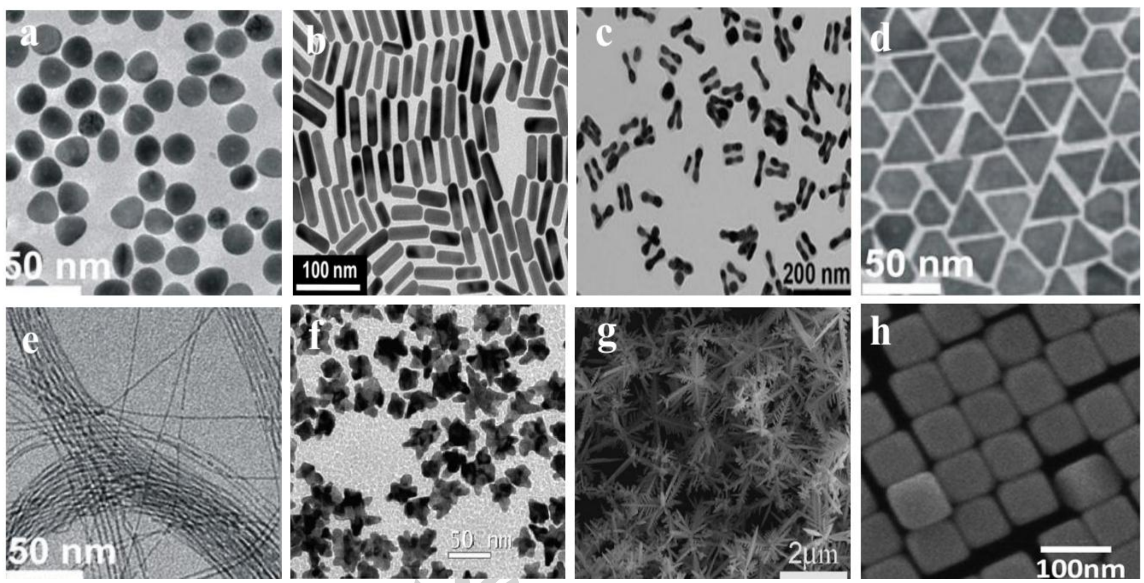


Fig. 1. (a-f) TEM images of AuNPs: a) quasi-spheres [20] b) nanorods [21] c) Nanodumbbells [22] d) triangular nanoprisms [20] e) Ultrathin nanowires [20] f) nanostars [23]; (g-h) SEM images of AuNPs: g) nanodendrites [24] h) nanocubes [25]. Copyright © American Chemical Society.

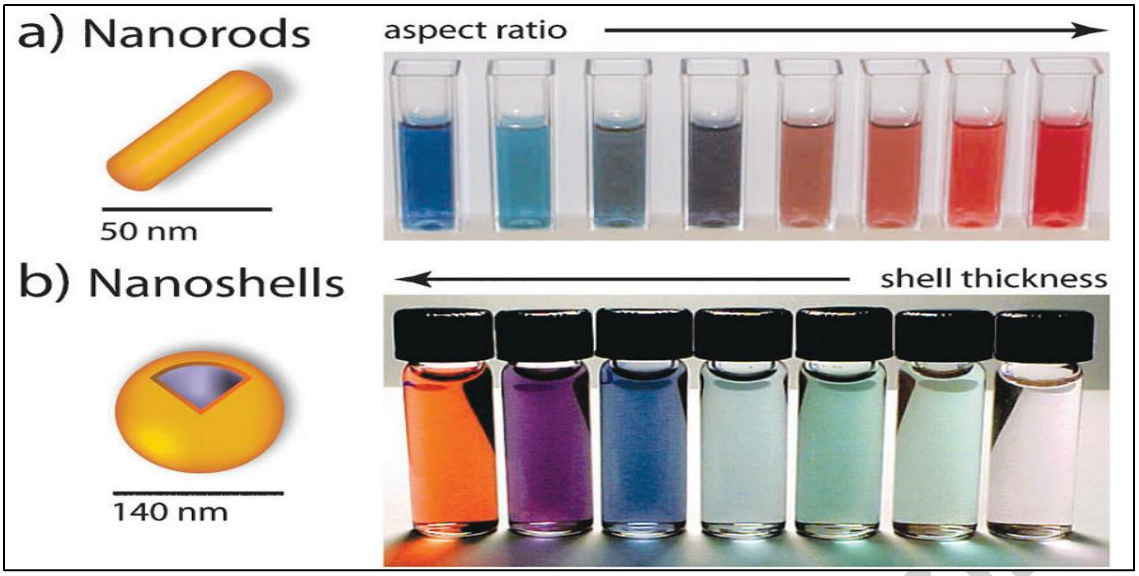


Fig. 2. Association of different morphologies and sizes of AuNPs with optical properties. (A) Gold nanorods, (B) Silica– gold core–shell nanoparticles [26].

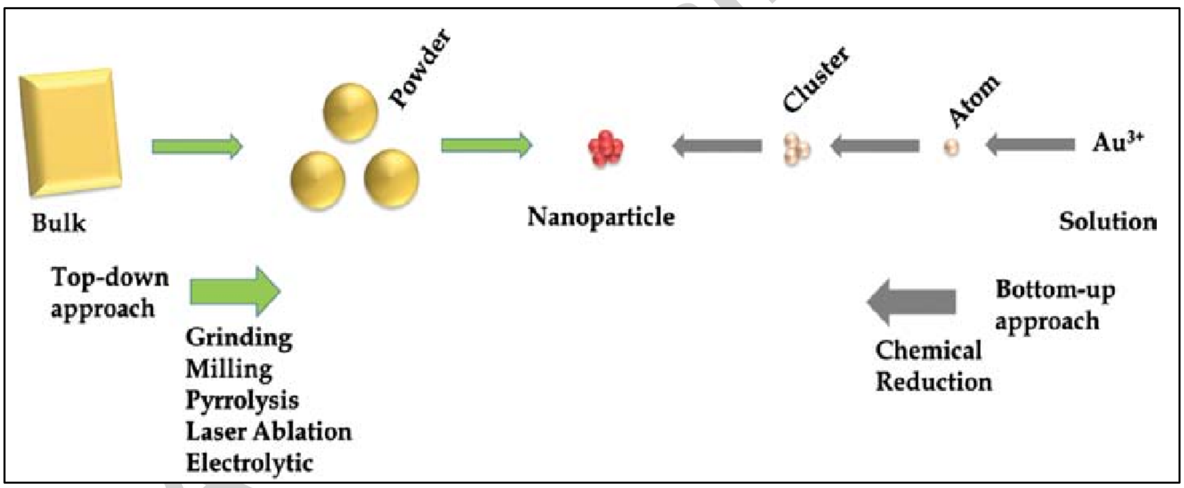


Fig. 3. Basic approaches for nanoparticle preparation [4].

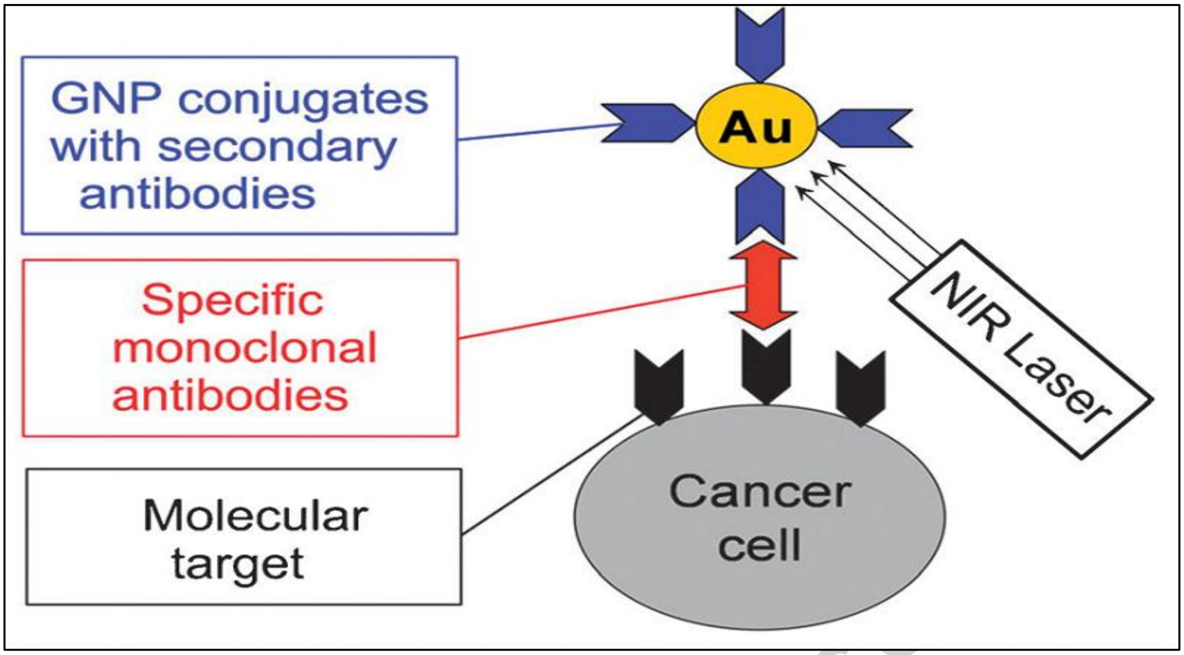


Fig. 4. Scheme for a PTT employing active delivery of AuNPs to cancer cells [79].

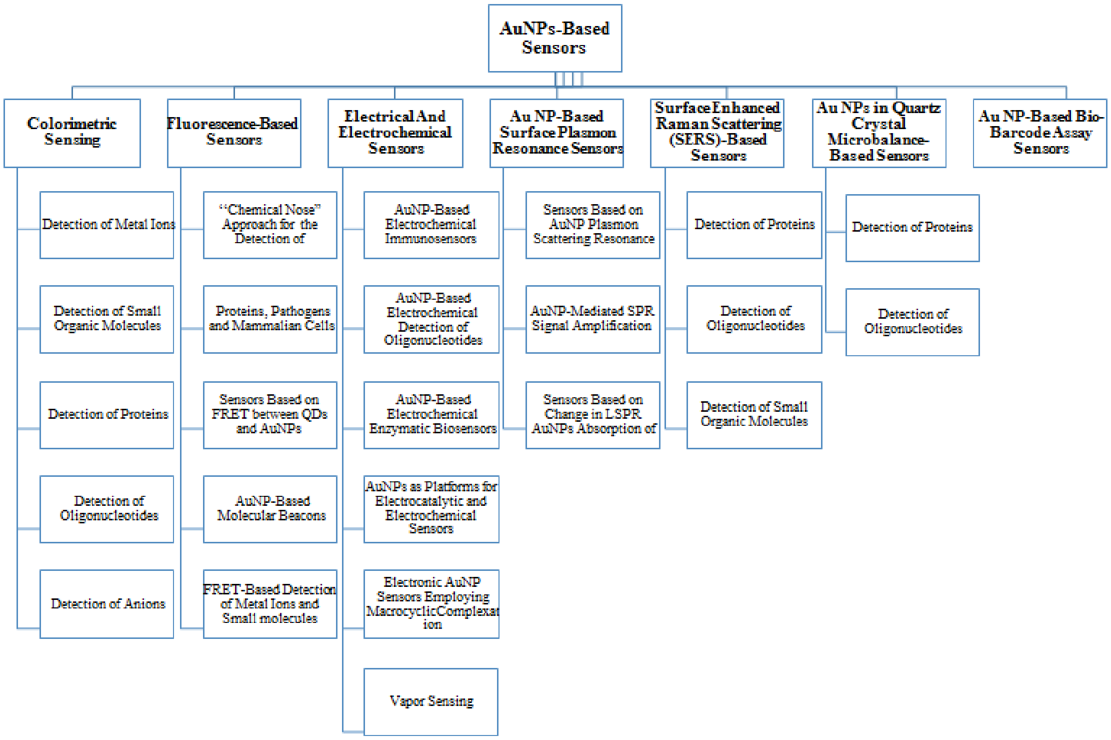


Fig. 5. Summary of different types of gold nanoparticles biosensors; utilizing the explicit physicochemical properties of this nanoparticles, various sensors can be designed.

Table 1 Biological resources for AuNPs synthesis.

Microorganism	Specious Name	Size range (nm)	Shape of AuNPs	Application	Ref
Plant-based compounds and derivatives	*Panax ginseng*	10 – 40	Spherical		[38]
	Cacumen platycladi	20-50	Spherical, triangular/hexagonal		[39]
	Plumbago zeylanica	>100	Spherical, triangles, hexagons	Antibacterial activity against Gram-negative and Gram-positive bacteria	[40]
	Abelmoschus esculentus	45–75	Spherical	Antifungal activity against *Puccinia graminis tritci, Aspergillus flavus, Aspergillus niger* and *Candida albicans*	[41]
	Hibiscus sabdariffa	25-30	Spherical	Selective toxicity towards U87 glioblastoma multiforme cell line under normal and hyperglycemic condition	[42]
	Cucurbita pepo L. leaves	10–15	Spherical		[43]
	Morinda citrifolia	12.17-38.26	Spherical	High potential for use in the treatment of anticancer, antidiabetic	[44]
	Eucommia ulmoides	~ 20	Spherical	Excellent catalytic activity	[45]
	Trigonella foenum-graecum	15-20	Spherical	Good catalytic activity for the reduction of 4-nitrophenol to 4-aminophenol by excess NaBH4	[46]
	Zingiber officinale	10	Spherical		[47]
	Hibiscus rosa sinensis	~14	Spherical, triangular		[48]
	Rosa hybrida	10	Cubic	High potential for use in biological applications	[49]
	Euphorbia hirta L.	6-71	Spherical	Antibacterial activity of the green synthesized Au NPs against bacterial strains of *Escherchia coli, Pseudomonas aeroginosa* and *Klebsiella pneumonia*	[50]
	Abelmoschus esculentus	62	Spherical	Antifungal activity	[41]
	Cassia auriculata	15–25	Spherical,hexagonal, triangular	May promote anti-hyperglycemic	[51]
	Couroupita guianensis, Aubl.	26 ± 11	Cubic	antioxidant activity	[52]
	Terminalia arjuna.	20-50	Spherical	Enhance the mitotic cell division and pollen germination activity	[53]
	Mentha piperita	>100	Spherical	Antibacterial activity against clinically isolated pathogens	[54]
Bacteria	*Klebsiella pneumoniae (MTCC- 4030)*	10 - 15	Spherical	Antibacterial activity against *Escherichia coli*	[55]
	Klebsiella pneumoniae	35-65	Spherical	Medical and pharmaceutical applications	[56]
	Geobacillus sp. strain ID17	5–50	Quasi-hexagonal	Potential application of this microorganism in bioremediation of gold-bearing waste	[57]
	Klebsiella pneumoniae	35-65	Spherical		[56]
	Escherichia coli K12	50	Spherical	Catalytic activity	[58]

Table 1 (*continued*)

	Acinetobacter sp. SW 30	20 ± 10	Triangle, rod, spherical		[59]
	Bacillus stearothermophilus	5-30	Spherical, triangular	Detect toxin A (TOA) of *Clostridium difficile* based on an aptamer	[60]
	Bacillus Subtilis	10-15	Cubic	Antimicrobial agents in packaging applications	[61]
Fungi	*Aspergillus sydowii*	8.7–15.6	Spherical		[62]
	Rhizopus oryzae	43 ± 19	Flower-like	Stable in different physiological buffers and hemocompatible	[63]
	Penicillium citrinum	60–80	Spherical	Antioxidant activity in pharmaceutical and cosmetic industries	[64]
	Alternaria sp.	7–13 and 15–18 and 69-93	Quasi-spherical, Spherical, square, rod, pentagonal, hexagonal		[65]
	Neurospora crassa	32	spherical		[66]
Algae	*Spirulina platensis*	~5	Spherical	Antibacterial activity against Gram positive organisms	[67]
	Turbinaria conoides and Sargassum tenerrimum	27–35	Spherical	Catalytic activator	[68]
	Sargassum swartzii	35	Spherical	Anticancer for HeLa cells	[69]
	Stoechospermum marginatum	18.7-93.7	Hexagonal, triangle	Antibacterial activator	[70]
	Cystoseira baccata (CB)	8.4 ± 2.2	Spherical	Activity in colon cancer cells (cytotoxic effect against colon cancer cells)	[71]
	Tetraselmis kochinensis	5–35	Spherical	Non toxic	[72]
	Kappaphycus alvarezii	10-40	Spherical		[73]
Yeast	*Instant high-sugar dry yeasts*	Dependent on PH	Triangle, truncated triangle, hexagon Nano plates	Plasmonic Properties	[74]
	Yeast extract mannitol (YEM)	4-20	Spherical		[75]
	Baker's yeast (Saccharomyces cerevisiae)	~5.0 ± 2.0	Spherical	Anticancer evaluation against Ehrlich ascites carcinoma cells	[76]
	Hansenula polymorpha	20 – 40	Spherical		[77]
Viruses	*tobacco mosaic virus (TMV)*	10–40			[78]

Table 2 Various methods were for Au NRs Synthesis [9].

	synthetic techniques	**Type of Au NRs**	
I	Aqueous wet-chemical CTAB-mediated synthetic procedures	crystalline nanorods	single-crystalline structure
			pentahedrally-twinned structure
II	Reduction of gold inside a sort template	polycrystalline structures	

III	Synthesis in organic solvents	ultrathin rods and wires

Table 3 Au NRs properties and their applications in biosensing.

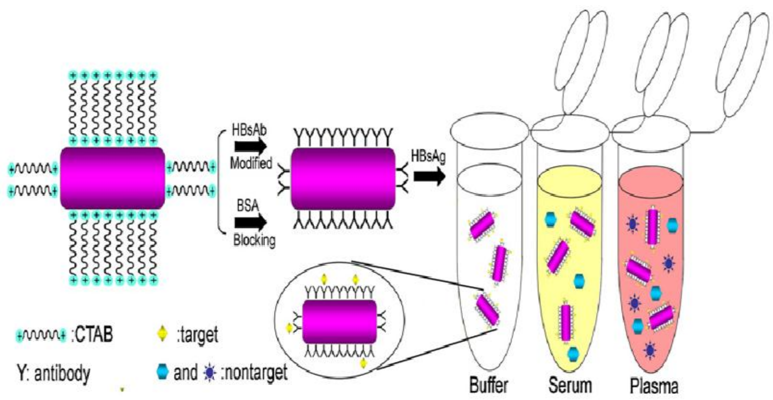
Properties	**Agent or pathogen**	**Schematic representation of Au NRs biosensor**	**Ref**
Localized surface plasmon resonance (lspr)	Hepatitis B virus	 The AU NRs biosensor based on the localized surface plasmon resonance (LSPR) behavior was designed to detect the hepatitis B surface antigen (HBsAg) which indicates active viral replication of hepatitis B virus (HBV).	[142]

Table 3 (*continued*)

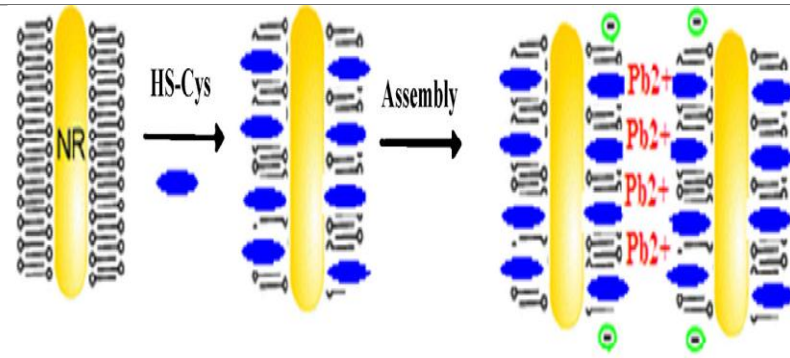
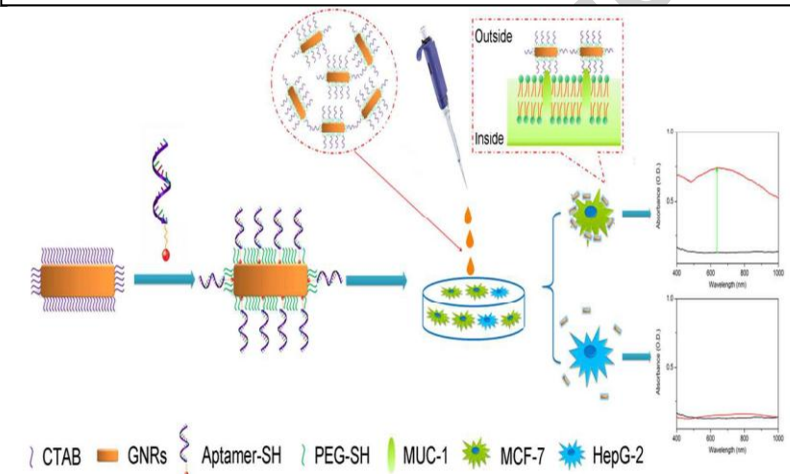
Lead	 Aggregation-based Au NRs probe has been developed for the detection of Pb^{2+} in aqueous solution, based on the fact that Pb^{2+} ions induce assembly mediated signal enhancement of cysteine-functionalized Au NRs.	[144]
MCF-7 breast cancer cells	 After the modification by MUC-1 aptamers, the special reaction between functionalized AU NRs and target cells were detected by LSPR spectra. Because of the anisotropy of AU NRs, the longitudinal LSPR band was demonstrated to be more sensitive in reflecting the dispersion state of nanoparticles than the transverse one both experimentally and theoretically.	[145]

Table 3 (*continued*)

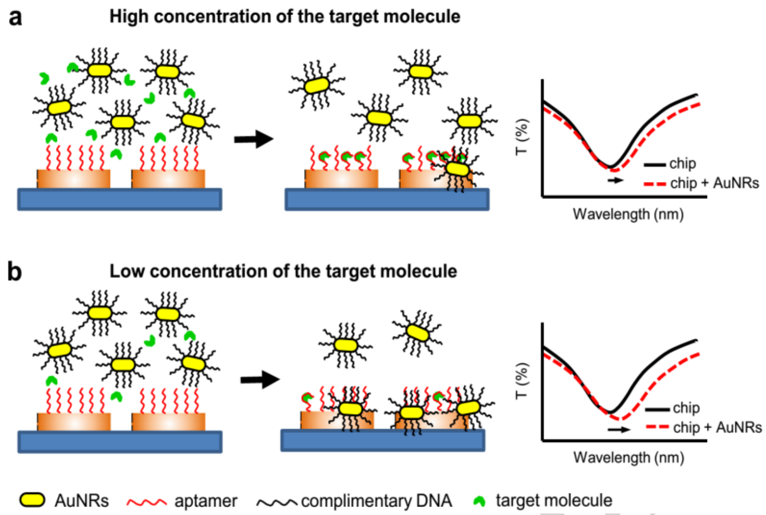
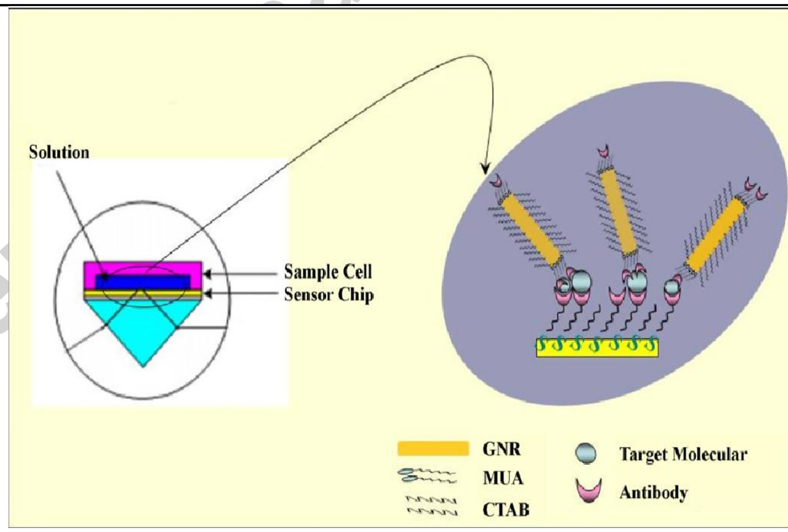
Interferon-γ	 Using the DNA-functionalized Au NRs to increase the spectral shift in LSPR sensing with the aptamer-functionalized LSPR chip; (a) When the concentration of the target molecule is high, the number of the Au NRs immobilized on the chip surface through DNA hybridization is reduced, and the LSPR shift induced by the Au NRs is small. (b) When the concentration of	[146]
E. coli O157:H7	 The diagram of combined target molecular to antibody with AU NRs in SPR sensor; AU NRs were used to enhance the sensitivity of the biosensor for *Escherichia coli O157:H7* in surface plasmon resonance (SPR) system.	[147]

Table 3 (*continued*)

<table>
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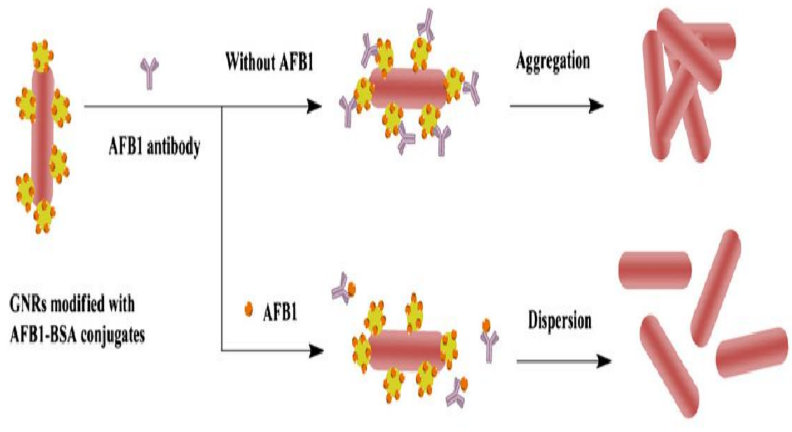
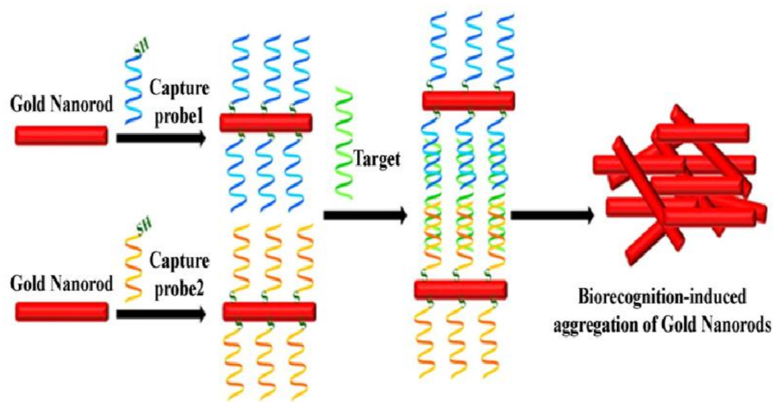
<td rowspan="2">Optical property</td>
<td>Aflatoxin B1 (mycotoxins produced by Aspergillus flavus and Aspergillus parasiticus)</td>
<td>



AFB1 sensing based on competitive dispersion of AU NRs; AU NR-AFB1–BSA (bovine serum albumin) conjugates aggregated after mixing with free antibodies, resulting in significant changes in absorption intensity; At the same time the existence of AFB1 molecules in samples caused dispersion of nanorods, as a result of competitive immune-reaction with antibodies.
</td>
<td>[143]</td>
</tr>
<tr>
<td>Chlamydia trachomatis</td>
<td>



Schematic representation of DNA hybridization detection with Au NRs. Specific target recognition induces aggregation of gold nanorods.
</td>
<td>[141]</td>
</tr>
</table>

Table 3 (*continued*)

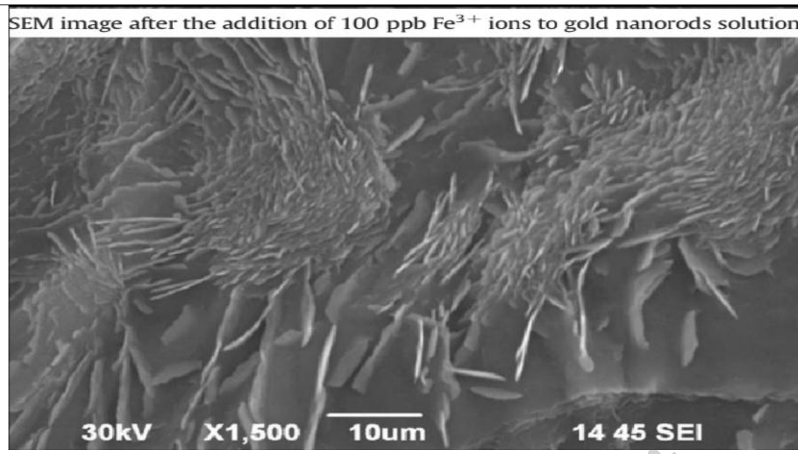
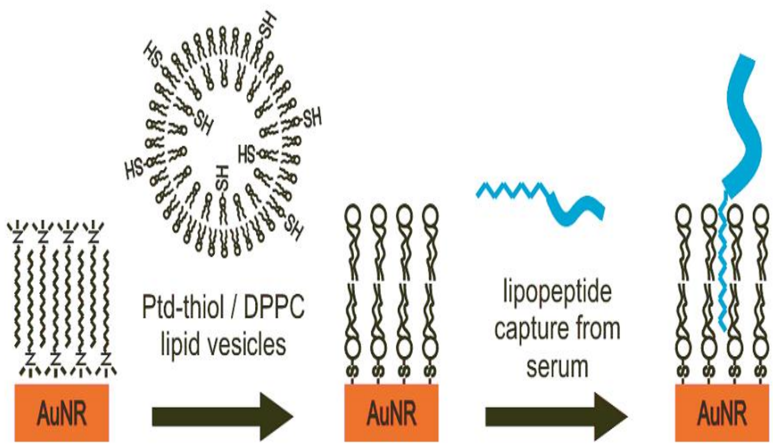
Fe(III) ions	 SEM image after the addition of 100 ppb Fe^{3+} ions to gold nanorods solution. A novel and systematic method for sensitive detection of Fe^{3+} ions in aqueous media using Au NRs as nano sensors is presented. The interaction of Fe^{3+} ions with Au NRs was investigated by surface enhanced Raman scattering (SERS) using crystal violet (CV) molecule.	[148]
lipophilic analytes	 The production of lipid-capped Au NRs was carried out by replacing the CTAB bilayer with a lipid layer using small unilamellar vesicles containing lipids with a thiol head group. The lipid-capped Au NRs can be used for the capture of lipophilic analytes from complex solutions for label-free biosensing applications.	[149]

Table 3 (*continued*)

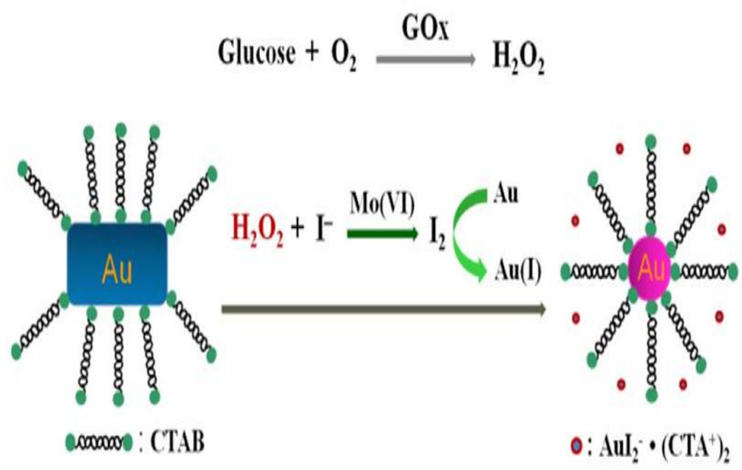
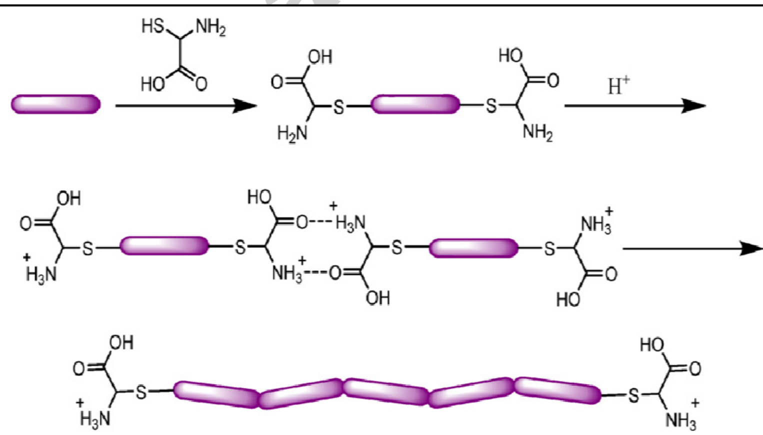
	Glucose	 The mechanism of the AU NR-etching-based glucose sensor; AU NRs are etched by I2 along the longitudinal direction due to less surface passivation and/or the higher reaction activities at the tips of AU NRs. The enzymatic-like etching of GNRs result in the shortening of AU NRs with increase in glucose concentration. The shortening of AU NRs leads to a blue-shift of the LSPR of AU NRs, accompanied by a color change from blue to red	[150]
self-assembly	Cysteine	 Detection of cysteine using self-assembly of gold nanorods in the acidic medium; This methodology is based on the end-to-end assembly of gold nanorods and it is very sensitive due to the useful formation of the gold nanorods chain in the presence of cysteine under acidic aqueous solution.	[151]

Table 3 (*continued*)

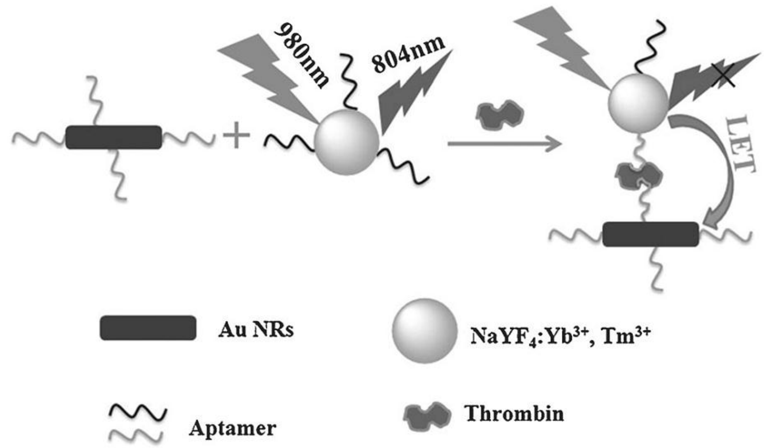
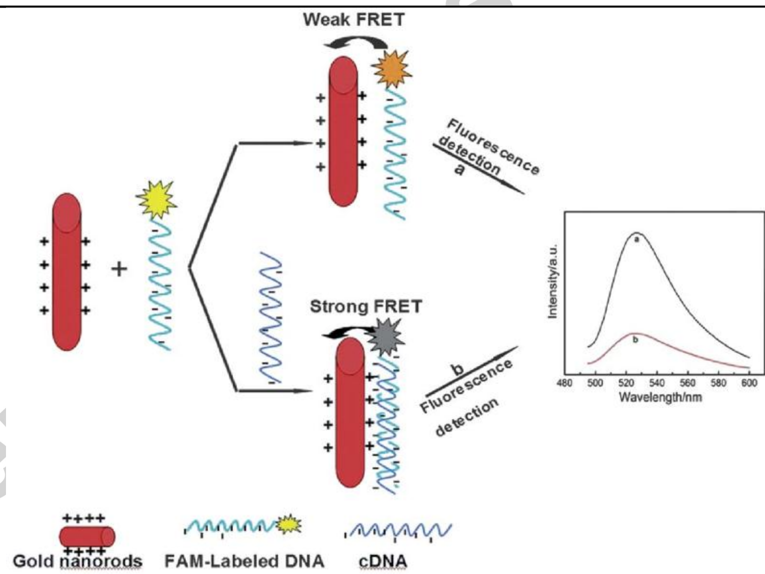
luminescence energy transfer (LET)	Thrombin	 Two probes (UCNPs-TBA15 and Au NRs-TBA29) were obtained by functionalization of the poly (acrylic acid) (PAA)-modified NaYF 4: Yb3+, Tm3+ UCNPs and the CTAB-stabilized Au NRs with thrombin aptamers.	[152]
Fluorescence resonance energy transfer	Hepatitis B virus DNA	 Schematic representation of the strategy for DNA hybridization detection; The Au NRs-based fluorescent biosensor was designed for the detection of HBV sequences, and FAM-ss DNA was selected as the probe DNA.	[153]

Table 3 (*continued*)

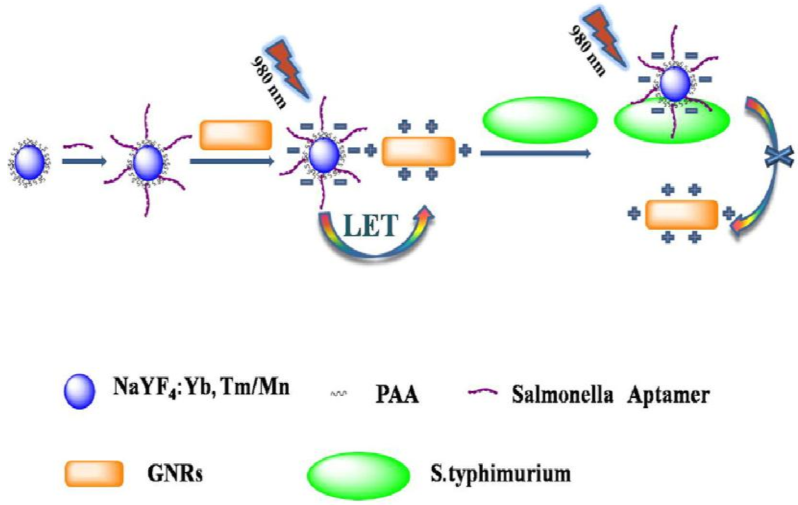
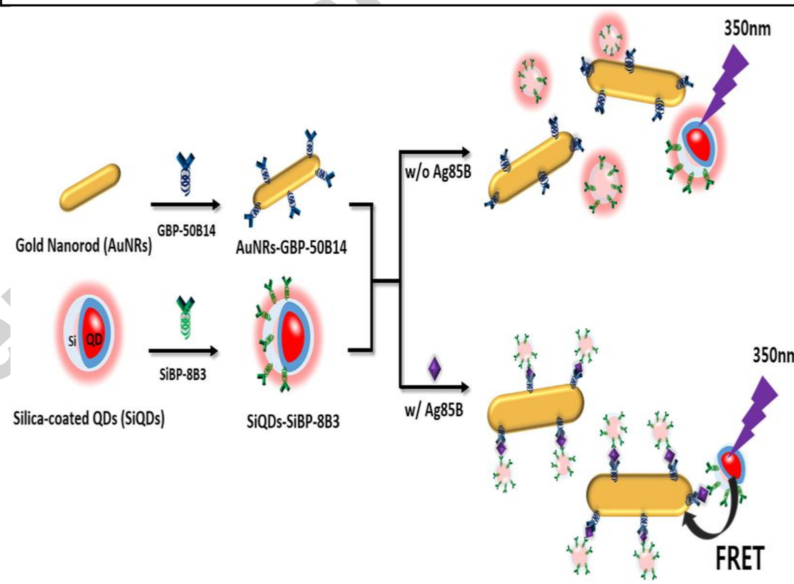
Salmonella typhimurium	 The fabrication process of bio functionalized nanoparticles and principle of the performed bioassay; Au NRs served as the acceptor (positively charged). On the basis of the electrostatic interactions, the donor and the acceptor were brought into close proximity, which resulted in luminescence quenching. Subsequently, *S. typhimurium* was added to the system.	[154]
Mycobacterium tuberculosis Ag85B	 The fluorescent analysis method for the detection of secreted antigen from *M. tuberculosis* based on sandwich assay via antigen-antibody interaction using Au NRs and SiQD; The secreted antigen Ag85B and fused recombinant antibodies GBP-50B14 and SiBP-8B3 were employed for the detection of the active *M. tuberculosis*.	[155]

Table 3 (*continued*)

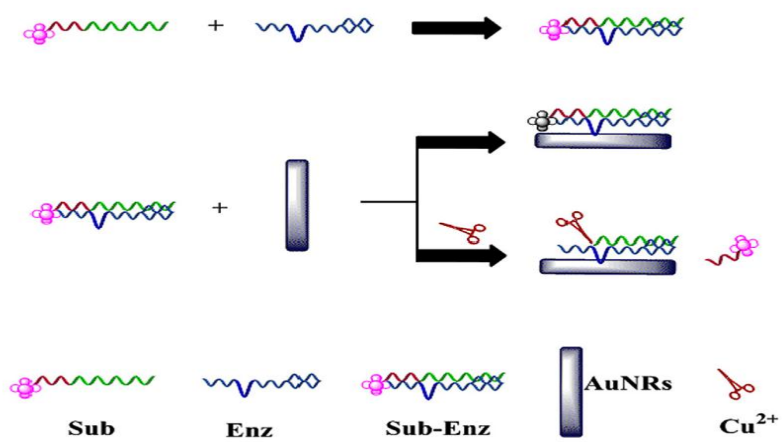
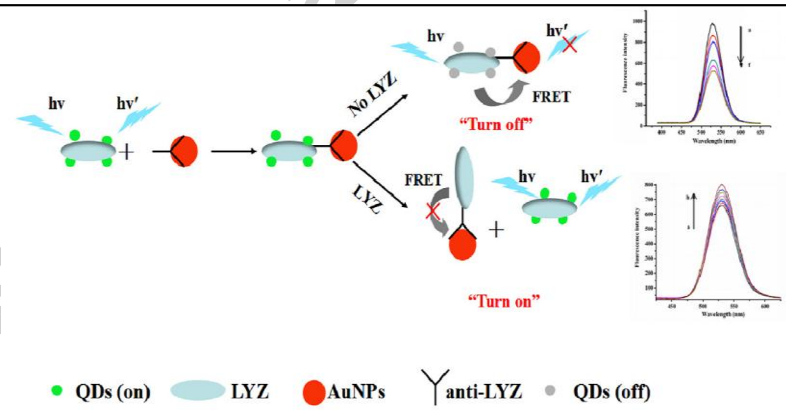
Copper(II)	 The strategy of Cu^{2+} ions detection using Cu^{2+} dependent DNA-cleaving DNAzyme via Au NRs-based fluorescence resonance energy transfer assay; In the absence of Cu^{2+}, the fluorescence of TAMRA was significantly quenched. Upon the presence of Cu^{2+}, the DNA was cleaved at the guanine base site into two parts. The cleaved short TAMRA-labeled DNA fragment has a lower charge density than the Sub-Enz duplex, which weakened the electrostatic interaction between DNA and Au NRs and the fluorescence intensity of the system recovered.	[156]
Lysozyme	 Principle of the fluorescence switch control system. the strong fluorescence of LYZ-modified Quantum Dots (QDs-LYZ) could be effectively quenched by gold nanoparticle (Au NPs) modified with antibodies against LYZ(anti-LYZ) due to fluorescence resonance energy transfer (FRET) between QDs-LYZ and anti-LYZ-AuNPs. The fluorescence can be reversibly recovered by LYZ (on state) owing to specific competitive interactions between LYZ, QDs-LYZ and anti-LYZ-Au NPs. The interaction of QDs-LYZ with anti-LYZ-Au NPs was studied by absorption, fluorescence spectroscopy.	[157]

Table 3 (*continued*)

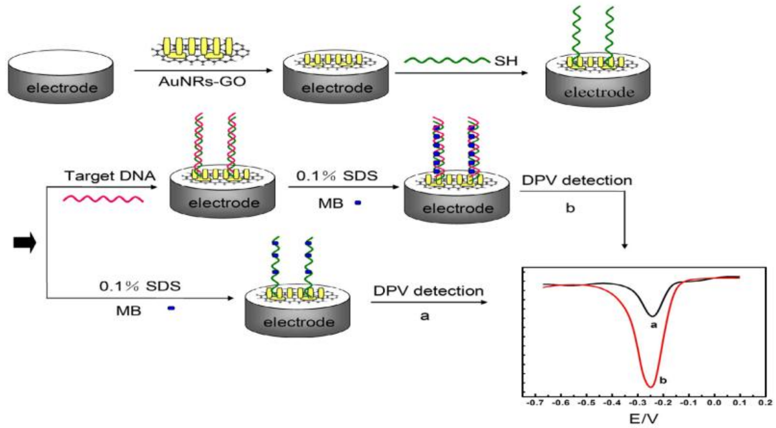
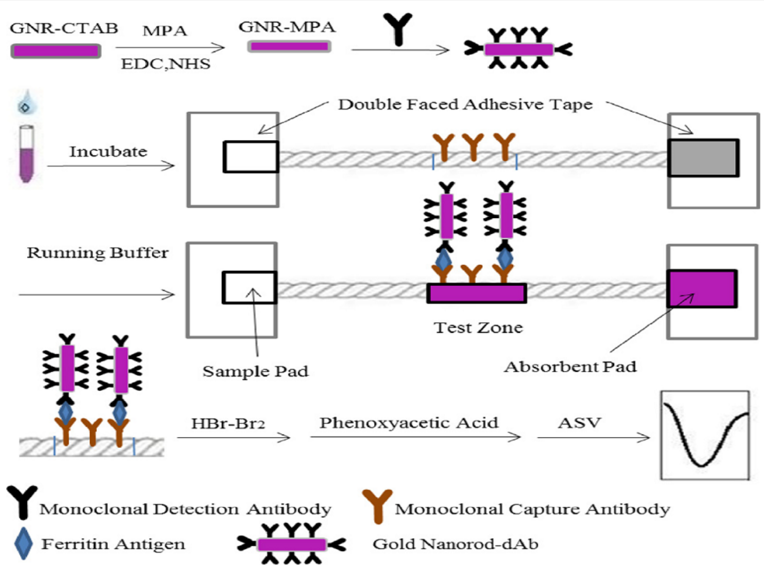
	DNA	 The DNA biosensor fabrication procedure; MB, methylene blue; SDS, sodium dodecyl sulfate; DPV, differential pulse voltammetry. An electrochemical sensor for sensitive and selective DNA detection was constructed based on Au NRs decorated graphene oxide (GO) sheets.	[158]
Electrical property	Human ferritin	 The principle of the nature cotton thread based immunoassay device for electrochemical detection of ferritin. The solution of GNR-dAb-Ferritin complexes was applied to the sample pad, and immediately migrated along the cotton thread to cAb, which was pre-immobilized as the test zone of the cotton thread, where the ferritin antigen is captured to form sandwich AU NR-dAb-Ferritin cAb complexes. Because of the accumulation of AU NR complex, a purple band would appear on the test zone.	[159]

Table 3 (*continued*)

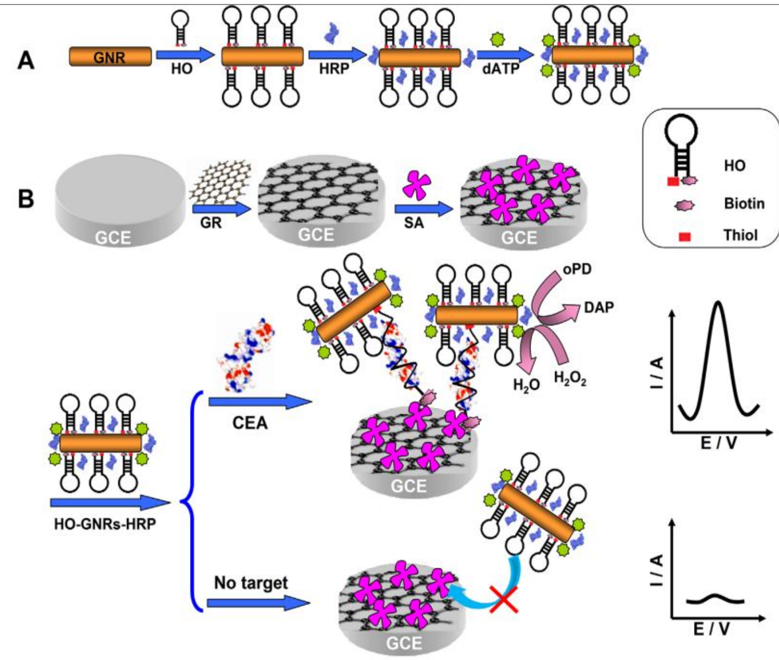
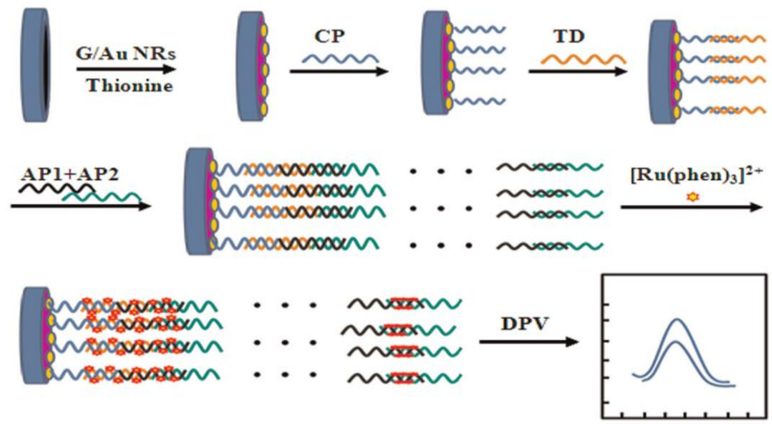
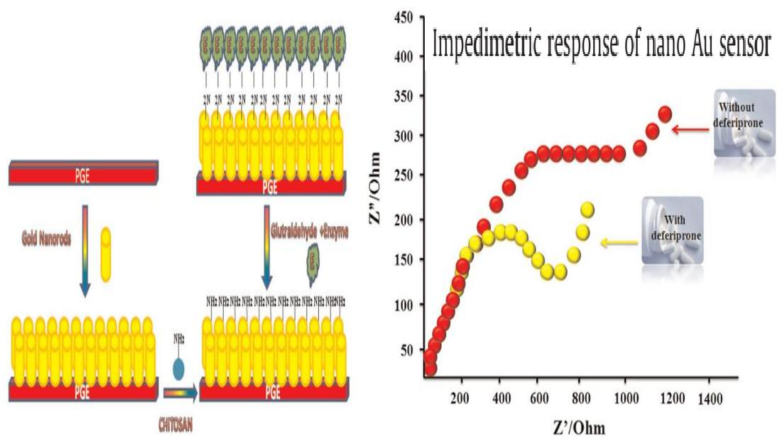
Carcinoembryonic antigen	 (A) Modification procedure of HO-GNRs-HRP conjugate. (B) Schematic illustration of the assembly process of SA-CS/GR/GCE and electrochemical sensing strategy for the detection of CEA: In the presence of target CEA, the binding reactions of CEA with the loop portions of the HOs caused HOs' loop-stem structure opened and exposed the biotins, and then HRP-AU NRs-HO conjugates were captured on graphene and streptavidin modified electrodes via the reaction between the exposed biotins and preimmobilized streptavidins. The accumulation of HRP effectively catalyzed the hydrogen peroxide-mediated oxidation of o-phenylenediamine to generate an electrochemical reduction current for CEA detection.	[160]

Table 3 (*continued*)

Human papillomavirus (HPV)	 The long-range self-assembled DNA electrochemical biosensor; CP was immobilized on G/Au NR/PT GCE both through strong Au–S bond, and the electrostatic interaction with the positively charge Au NRs. The presence of MCH aimed to block the nonspecific binding sites. Subsequently, one terminal of TD was immobilized on the electrode via hybridizing with CP, and the other terminal of TD hybridized with AP1. AP2 was introduced to hybridize with AP1. The liberated target triggered the connection of a long DNA nanostructure to CP. Numerous $[Ru(phen)3]^{2}+$ were bound to the DNA nanostructure with negative charges via electrostatic interaction and enhanced significantly electrochemical signals.	[161]
Anti-HIV drug (deferiprone)	 The stepwise fabrication of the nano Au sensor biosensor. AU NRs deposited onto pencil graphite electrode (PGE) has been utilized for covalent immobilization of horse radish peroxidase (HRP), via glutaraldehyde (Glu), for deferiprone detection using impedimetric technique.	[162]

Highlights

- Gold nanoparticles exhibit unique intrinsic properties.

- Au NRs have attracted many interests because they possess certain specific features.
- Different controllable particles shapes and sizes of AuNPs have been synthesized by chemical, physical and biological methods.
- Various biomedical applications could be done by applying the physicochemical properties of AuNPs.