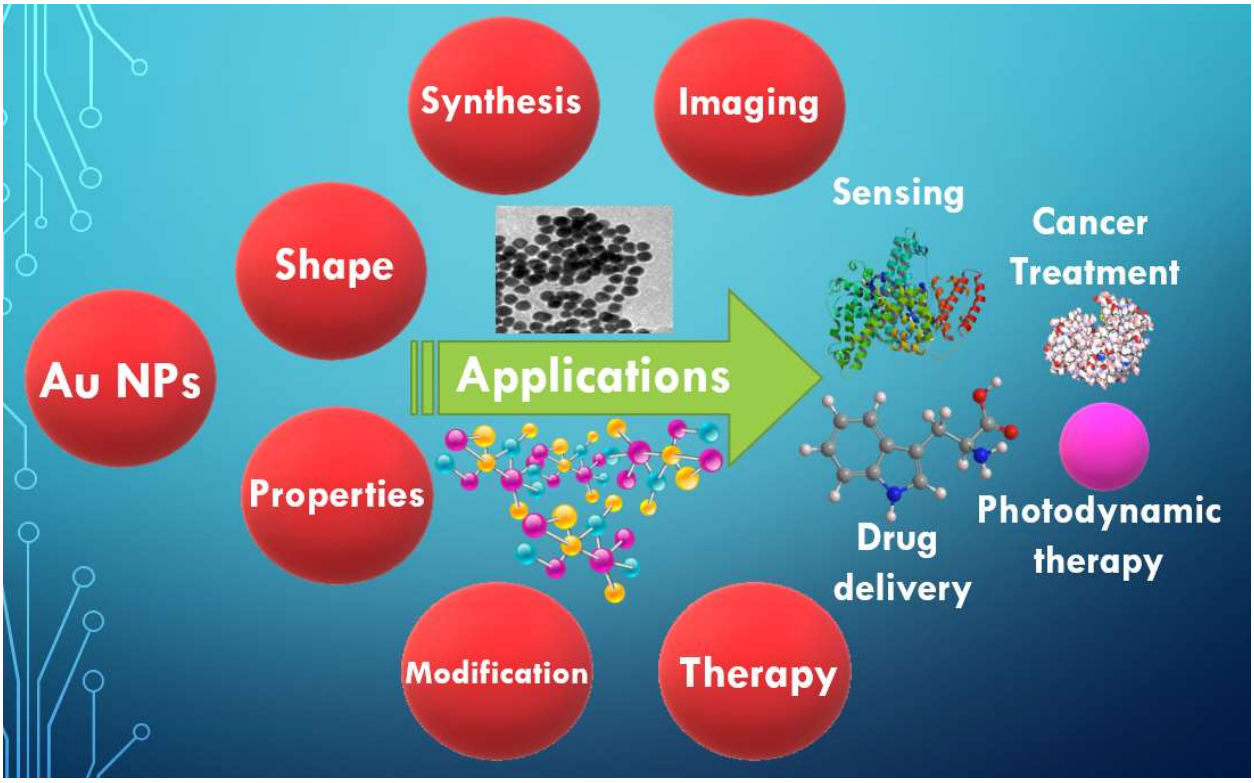
JOURNAL of QASSIM UNIVERSITY FOR SCIENCE
©2023 Qassim University [E-ISSN: 1658-9610]
Vol. 2, Issue 1, pp 51-73 (Aug 2023)
JQUS

Gold Nanoparticles: A Critical Review on Synthesis and Significant Applications

Sayed M. Saleh

Department of Chemistry, College of Science, Qassim University, Buraidah 51452, Saudi Arabia;

E.saleh@qu.edu.sa (S.M.S.



ABSTRACT

The creation of artificial nanoparticles has led to recent progress in nanotechnology. The biomedical field has made extensive use of metallic nanoparticles, with particular emphasis on gold nanoparticles (AuNPs). As a result of the crucial role they play, sphere and gold nanorods (AuNPs) have recently garnered a lot of interest. Their unique optical, electronic, physicochemical, and surface plasmon resonance (SPR) properties, which can be tuned by adjusting particle characteristics like size, shape, and environment, along with their amenability to synthesis and functionalization, have led to a wide range of applications in biomedicine, including sensing, targeted drug delivery, imaging, photothermal and photodynamic therapy, and the modulation of two-photon absorption and emission. In this review, we had a look at how to make Au NPs and discussed their many uses, notably in the field of biological sensing.

Keywords

AuNPS; Synthesis; Surface Modification; Therapy; Sensing.

1. Introduction

Because their colors change with their form and aggregation, they are easily functionalized, gold nanoparticles, also known as Au NPs, are good platforms for creating colorimetric biosensors. This is because Au NPs can be easily functionalized. During the last 10 years, a wide range of biosensors has been designed to take advantage of the magnitude of color changes that occur when nanoparticles either collect or disperse in the presence of analytes. The fact that the behavior of the systems must be both repeatable and predictable is of the utmost significance in designing these approaches. In recent years, considerable progress has been made in understanding the interactions between a broad variety of substrates and AuNPs, and how these interactions may be exploited as colorimetric reporters in biosensors.

Nevertheless, despite these advancements, only a small number of biosensors have been put into operation to detect analytes in biological samples. Moving biosensors from the proof of concept stage to the commercial market requires significant long-term reliability and shelf life testing, as well as adjusting protocols and design elements to make the biosensors user-friendly and risk-free for the general public. As new innovations are brought forward to enhance existing designs'

analytical performances and usability, the next decade will witness the adoption of user-friendly biosensors for point-of-care and medical diagnostics. These developments are expected to take place in the next decade. This paper explores the processes behind using Au NPs as colorimetric biosensors and the tactics, recent advancements, and prospects for the field.

2. The synthesis of gold nanoparticles

It has been documented how to synthesize gold nanoparticles using a variety of chemical and physical processes. The production of gold nanoparticles (AuNPs) with size, stability, and functionality that can be tuned has been the focus of significant effort over the last two decades [1-6]. Despite this, there has been a growing interest in most chemical technique because it is better than physical approaches in terms of scalability, repeatability, and adaptability. The use of wet chemistry in aqueous and organic solutions is an effective method for synthesizing gold nanoparticles (NPs) of varied sizes and functionalities [7].

2-1 The synthesis process based on Citrate reduction

During the standard procedure that Turkevich established recently, au compounds are reduced by adding citrate as a reducing agent. This leads to the nucleation of seeds, which is then followed by the production of crystals. Turkevich's technique was standardized in 1971. The process through which the sources transform into NPs [8-12]. The reaction is commonly carried out at a temperature of 100 degrees Celsius with high-speed agitation to reduce the localized concentration of metal ions Au(III) and hasten the reaction's pace. Charged citrate ions act as a stabilizing agent, helping to stabilize already-formed gold nanoparticles.

It is possible to manufacture gold nanoparticles (AuNPs) with diameters that can be controlled by adjusting the molar ratio of sodium citrate to gold (III); for example, Au NPs with a size of 13 nm may be produced at a citrate/Au(III) molar ratio of 3.88 [13-16]. In the presence of a high citrate/Au(III) molar ratio, nucleation takes precedence, which leads to the creation of gold nanoparticles with a highly tiny size. However, in the presence of low citrate/Au(III) ratios, big Au NPs emerge because the development of Au seeds becomes predominant. Because of its ease of use and consistent results, this technique is the one that is used most commonly for the production of gold nanoparticles ranging in size from 5 to 100 nanometers.

2-2 The Brust–Schiffrin technique.

A powerful reductive agent, such as sodium borohydride, is often needed to create microscopic gold nanoparticles with a size of five nanometers or less. Although it is feasible to generate tiny gold nanoparticles (3.5 nm) using sodium borohydride, the propensity of the as-prepared gold nanoparticles to aggregate restricts both their ability to be stored and the uses to which they may be put. Utilizing the strong thiol-gold bond [17]. Within one minute, the color of the solution shifts from yellow/orange to brown due to the addition of sodium borohydride, in contrast to the reduction caused by the citrate. The size of as-formed gold nanoparticles (Au NPs) is typically between 1.5 and 5 nanometers. The extraordinary stability of these Au NPs may be attributed to the formation of a thiolate ligand shell on the surface of each gold core due to intensive interactions between thiol and gold.

3. Properties

3-1 Surface plasmon resonance in Au NPs

The localized surface plasmon resonance (LSPR) that comes from the oscillation of conduction electrons at the surface of Au NPs in response to an incoming electromagnetic field is one of the optical features of Au NPs that is considered to be among the most exciting and intriguing of all of their other qualities [18,19]. Because the LSPR accounts for both absorption and scattering, most studies choose to measure something called extinction rather than absorbance. The electromagnetic field at the surface of the Au NPs makes it possible for the optical characteristics to be improved, which results in an extraordinarily LSPR band. This extinction coefficient is often several orders of magnitude higher than traditional organic pigments. The vivid colors of Au NPs may be attributed to the fact that the LSPR resonance of these nanoparticles is positioned in the visible spectrum. The fact that Au NP has both a high attenuation coefficient and a vivid color makes it easier to develop various optical sensing devices based on the material [20-22].

3-2 Colorimetric assays

The color of the colloid solution shifts from red to blue due to the accumulation of gold nanoparticles (Au NPs), however, the color shift may be reversed by redispersing the accumulated Au NPs, which causes the color to shift from blue to red. The color change that occurs during the aggregation or redispersion of Au NPs offers a broad platform for the absorption-based colorimetric detection of analytes that may directly or indirectly trigger the Au NP aggregation or redispersion. Because of their unusually high extinction coefficient and considerable distance-dependent LSPR absorption ability, gold nanoparticles (AuNPs) are well-suited for colorimetric analysis. In addition, the readout of Au NP-based assays may be viewed with the naked eye or recorded using a UV-vis spectrophotometer. Both of these methods are possible. As a result, numerous colorimetric chemo/biosensors based on Au NPs have been successfully fabricated for detecting inorganic ions, small molecules, oligonucleotides, and proteins (Figure 1).

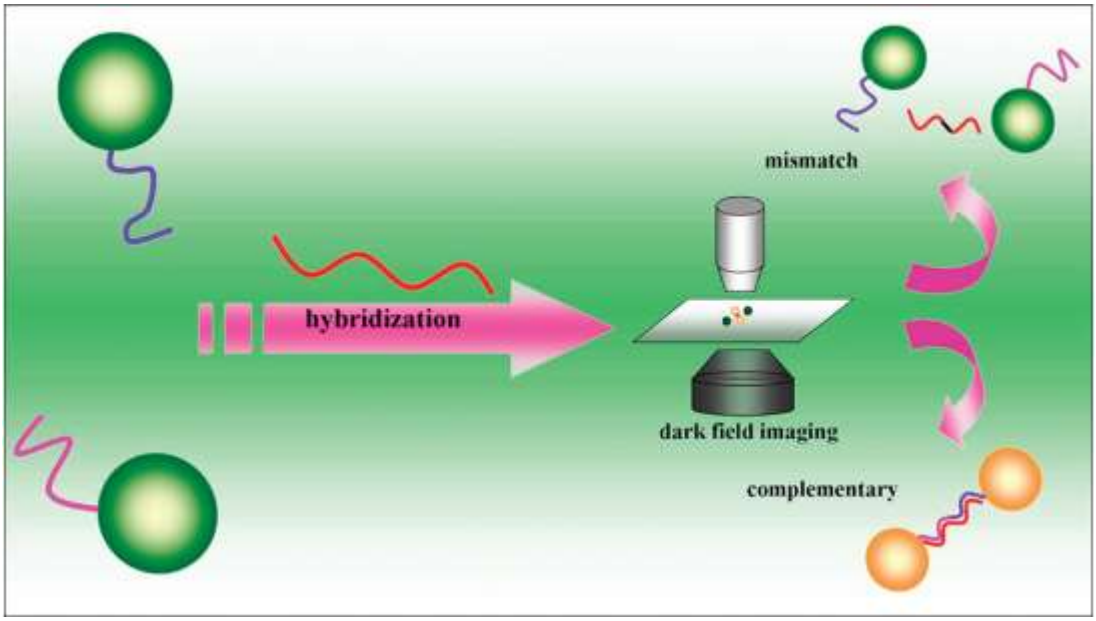


Fig. 1. DNA sandwich assay on single Au NPs. (ref. No. 23)

Colorimetric procedures on individual Au NPs, colorimetric detection generated by accumulation, and colorimetric detecting caused by disassembly are the three main types of these sensors [23-30].

3-3 Proteins.

Since aberrant quantities of protein or protein variation may be accompanied by illnesses and diagnostics emphasize accurate and rapid protein detection. A wide variety of ligand-functionalized Au NPs have been reported to detect proteins. These ligand-functionalized Au NPs work in one of three different ways: either protein-ligand binding induces Au NPs accumulation, protein-catalyzed ligand cleavage/polymerization induces Au NP aggregation or protein-promoted generation of product induces Au NP aggregation/growth. For example, several carbohydrate-functionalized gold nanoparticles (Au NPs) have been created to detect carbohydrate-binding proteins such as communis agglutinin 120 and lectins. These lectins are found in plants. By exploiting the biotin-specific interaction with streptavidin [31-35], biotin-modified Au NPs could detect streptavidin with a limit of detection (LOD) of just 24 nM. Protein-functionalized Au NPs have been utilized to detect various proteins [36-43]. These NPs trigger the regular protein-protein exchange, known as the antigen-antibody interaction. For instance, several antigens functionalized Au NPs were used to detect antigens with a significant limit of detection (LOD) values [44-47]. Chang et al. discovered susceptible platelet-derived growth factors (PDGFs) when they used aptamer-Au NP probes based on aptamer-protein interactions [48,49]. Using a combination of aptamer-modified Au NPs (13 nm) and fibrinogen-adsorbed Au NPs (56 nm), they could detect picomolar levels of PDGF with increased sensitivity. This identification method mediated by aptamers has also been used in detecting other proteins, such as thrombin [50-52].

Because of the strong catalytic efficiency, sensitive detection of thrombin was possible with a limit of detection (LOD) of 0.04 pM. They also used this technology to detect plasmin based on plasmin-induced fibrin structure breakdown. The LOD for this detection method in serum was found to be 0.4 nM. The concept has been used to analyze additional proteins, such as adenosine deaminase, methyltransferase, and acetyltransferase [53,54]. Hydrolysis products can directly trigger the aggregation of citrate-stabilized gold nanoparticles (Au NPs), which may result in a color change in the Au NPs solution. In light of this approach, acetylcholinesterase was readily identifiable using Au NPs as a detection method [55]. Thiocholine is produced when acetylcholinesterase catalyzes acetylthiocholine to form thiocholine. Thiocholine attaches to the citrate Au NP surface through Au–S interactions and causes aggregation of Au NPs via electrostatic attraction. A similar enzyme called S-adenosylhomocysteine hydrolase could be identified with a limit of detection (LOD) of 6 nM [56,57].

The production of homocysteine due to the hydrolysis of S-adenosylhomocysteine in the presence of S-adenosylhomocysteine hydrolase ultimately leads to the aggregation of the functional Au NPs. The use of exonuclease-assisted cascaded recycling amplification in building Au NP-based sensing systems has been done to increase the sensitivity of the detection of proteins (enzymes) [58,59]. In the absence of exonuclease, the hybridization of two ssDNA probes results in the formation of dsDNA, which in turn leads to the accumulation of Au NPs. Incorporating exonuclease causes the generated dsDNA to be digested, which then liberates the individual Au NPs into the solution. As a direct result, the solution's color shifts from blue to red. TATA-binding protein can form a compound with double-stranded DNA, which then blocks the digestion of the DNA. The limit of detection (LOD) for TATA-binding protein provided by this colorimetric test is 10 nM.81 The detection of thrombin with a sensitivity of 5.6 pM at the detection limit was made possible using magnetic nanoparticles in conjunction with the aforementioned method [60].

4. Applications of AuNPs

4-1 Sensing

Scientists are actively encouraging the development of novel low-cost and quick-to-apply analytical techniques. Highly sensitive and selective optical chemical sensors are capable of doing this. Careful consideration of the substrate's properties may boost optical chemical sensors' performance [61-69]. Chemical and biological sensing are two essential uses for gold nanoparticles (AuNPs). Utilizing the inherent properties, gold nanoparticles have been used as effective sensors for detecting various analytes, including metal ions, anions, and compounds such as saccharides, nucleotides, proteins, and toxins [70-73]. Figure 2 depicts a variety of nano biosensors that are based on the properties of Au NPs. The sensor has been built with consideration given to the varied features of Au NPs and the desired detection of these particles. Following the sensing approach, the Au NPs sensors may be colorimetric, fluorescence-based, electrical and electrochemical, surface plasmon resonance, surface-enhanced Raman scattering (SERS)-based, quartz crystal microbalance-based, or Bio-Barcode assay sensors [74,75]. The unique properties of Au NPs have been used in a variety of nano biosensor configurations. Due to the numerous and one-of-a-kind optical features that gold nanorods possess, they have attracted much interest in biosensing among

the many forms of AuNPs. The primary indicators for developing sensitive biosensors are variations in optical absorbance and the optical absorbance itself [76,77].

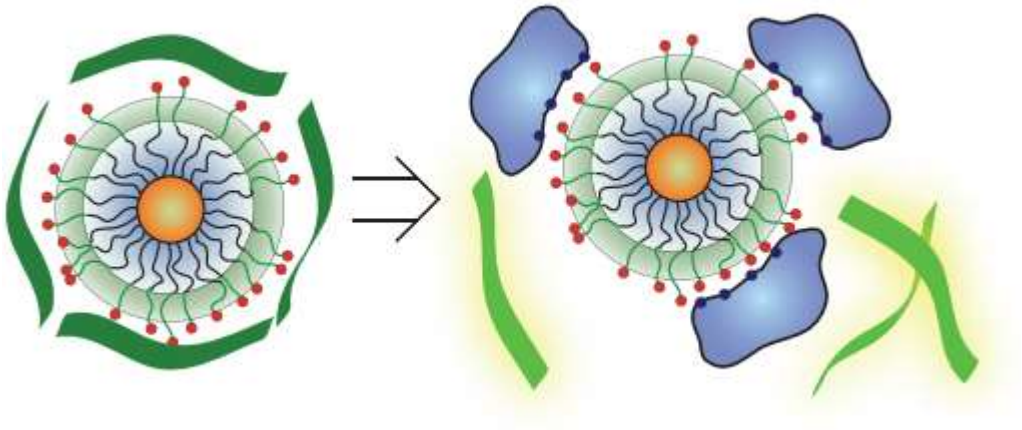


Fig. 2. Protein analyte (shown in blue) displaces quenched fluorescent polymer (shown in dark green; fluorescence off) and simultaneously restores fluorescence. (ref. No. 74)

4-2 Photodynamic therapy

Using photosensitizers as light-sensitizing agents and a laser (the wavelength associated with a peak of dye absorption) is the foundation of photodynamic therapy (PDT), which is well-recognized as an effective treatment for oncological disorders. PDT may also be used to treat specific skin or infectious diseases. Singlet oxygen and highly active free radicals produced due to the energy provided by photosensitizers may cause tumor cells to undergo apoptosis or necrosis [78,79]. In photodynamic treatment, uroporphyrin nanoparticles (Au NPs) have been exploited due to their ability to effectively quench fluorescence and absorb surface plasmon resonance (SPR). In addition, gold conjugation makes intracellular penetration easier because of gold's propensity to bond with thiols, disulfides, and amines [80]. This makes intracellular penetration easier.

4-3 X-ray imaging

As an X-ray contrast agent, Au NPs have garnered the majority of interest because they have a high X-ray absorption coefficient, are simple to manipulate synthetically, are non-toxic, and may have their surfaces functionalized to increase colloidal stability and targeted administration. Low-molecular-weight substances are often used as vascular contrast agents. Some examples of these substances are iodinated compounds. These iodinated aromatic compounds have a high water solubility, indicating they are not hazardous.

Despite this, the period spent in circulation in the blood is brief and removed from the body very quickly via the kidneys. As a result, an imaging window that is too short could call for numerous injections, putting the patient in danger of developing thyroid dysfunction. The obstacles have been easily overcome by Au NPs [81,82]. Due to the presence of essential qualities in Au NPs [83,84], the formation of an imaging window due to a longer vascular retention period than conventional agents has occurred.

4-4 Drug delivery

As was mentioned earlier, the many advantageous characteristics of AuNPs, including their superior optical and physicochemical properties, biocompatibility, functional flexibility, tunable monolayers, controlled dispersity, high surface area for loading the density of drugs, stability, and absence of toxicity, make them an effective nanocarrier for use in drug delivery systems (DDSs) [85,86]. These efficient nanocarriers can transport a wide variety of medications, including chemotherapeutic agents [87,88], small interfering RNAs (siRNAs), plasmid DNAs (pDNAs), and peptides [89,90], proteins [91,92], and plasmid DNAs (pDNAs). A recent study has shown that stable colloidal gold nanorods may be an effective agent for drug administration in addition to spherical nanoparticles. By circumventing the reticuloendothelial system (RES) clearance, PEGylated Au NRs can facilitate an adequate drug transfer. The second potential option is nanocages made of gold. Targeted medication delivery may be achieved by attaching cancer cell receptors to the surface of nanocages conjugated with bioactive molecules such as antibodies. Both Verigene (which has been authorized by the FDA) and Aurimmune (which is in Phase II) are examples of gold-based nanomaterials being developed for use in therapeutics [93,94].

4-5 Treatment for Cancer

Cancer is characterized by an unregulated proliferation of aberrant cells that may metastasize (spread to other body regions). Cancer cells become increasingly heterogeneous as the tumor develops because they begin to express a wider variety of markers. This variation raises the risk of tumor development, therapeutic resistance, metastasis, and recurrence [95-97]. In light of these considerations, fresh approaches to cancer diagnosis, therapy, and recurrence prevention are required. Cancer treatment, including detection, medication and gene delivery, and hyperthermia [98], are three areas where nanomedicine is showing significant promise today (Figure 3).

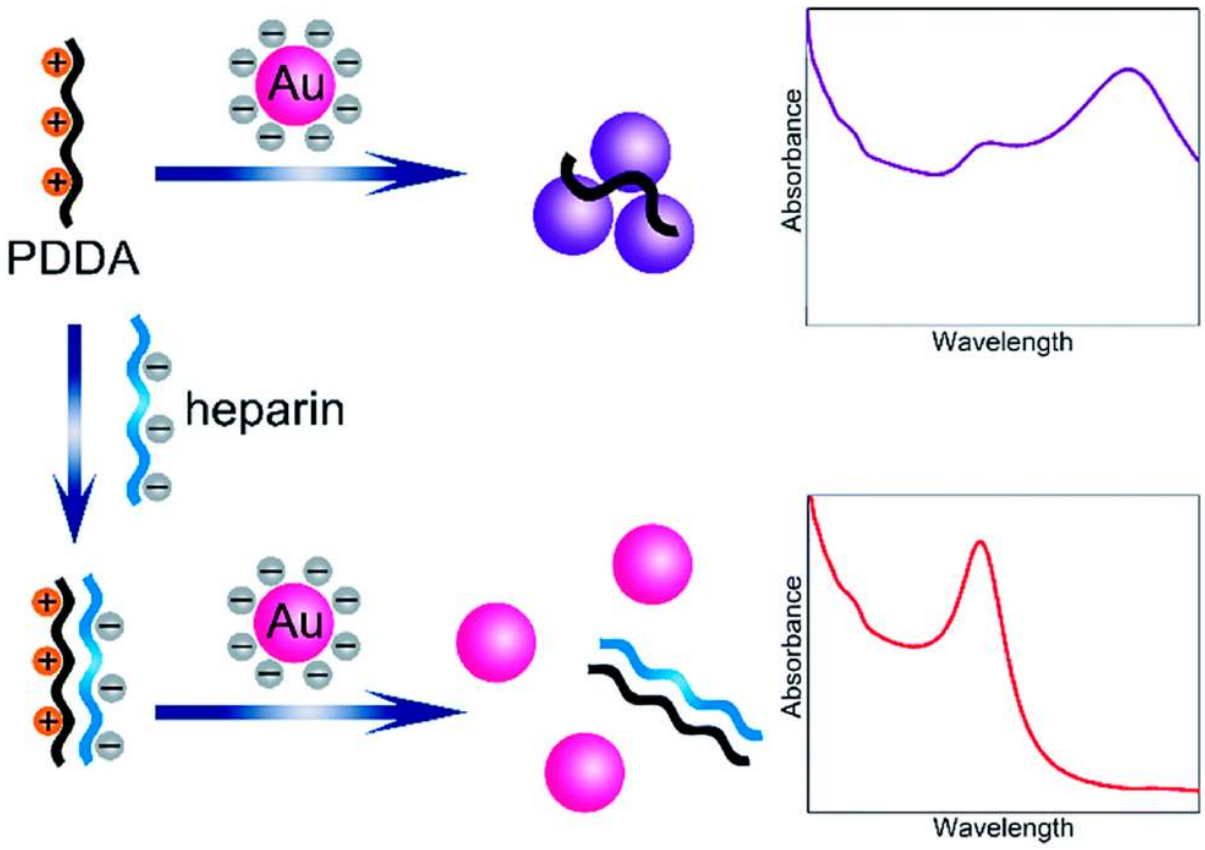


Fig.3. This diagram depicts the label-free colorimetric detection of heparin. (ref. No. 98)

Gold nanoparticles, particularly, are attracting much interest in cancer treatment because of their impressive set of features. Biosynthesized gold nanoparticles have been found to have in-vitro anticancer efficacy against many cancer types.

The CC50 value for cytotoxicity against HL-60 leukemia cells was 5.14 M for freshly produced Au NPs from the aqueous floral extract of C. guianensis. DNA fragmentation was used to establish that apoptosis was induced by the biosynthesized Au NPs in HL-60 cells [99]. Some medicinal anticancer plants were employed to manufacture Au NPs with a potent cytotoxic impact on cancer cells. The biosynthesized Au NPs had antitumor efficacy that increased with increasing doses. The formation of reactive oxygen species (ROS), mitochondrial malfunction, and the activation of intrinsic and extrinsic apoptotic pathways are all possible methods by which Au NPs exert their anti-cancer effects. The protein structure is altered, and the cell cycle is stopped [100,101].

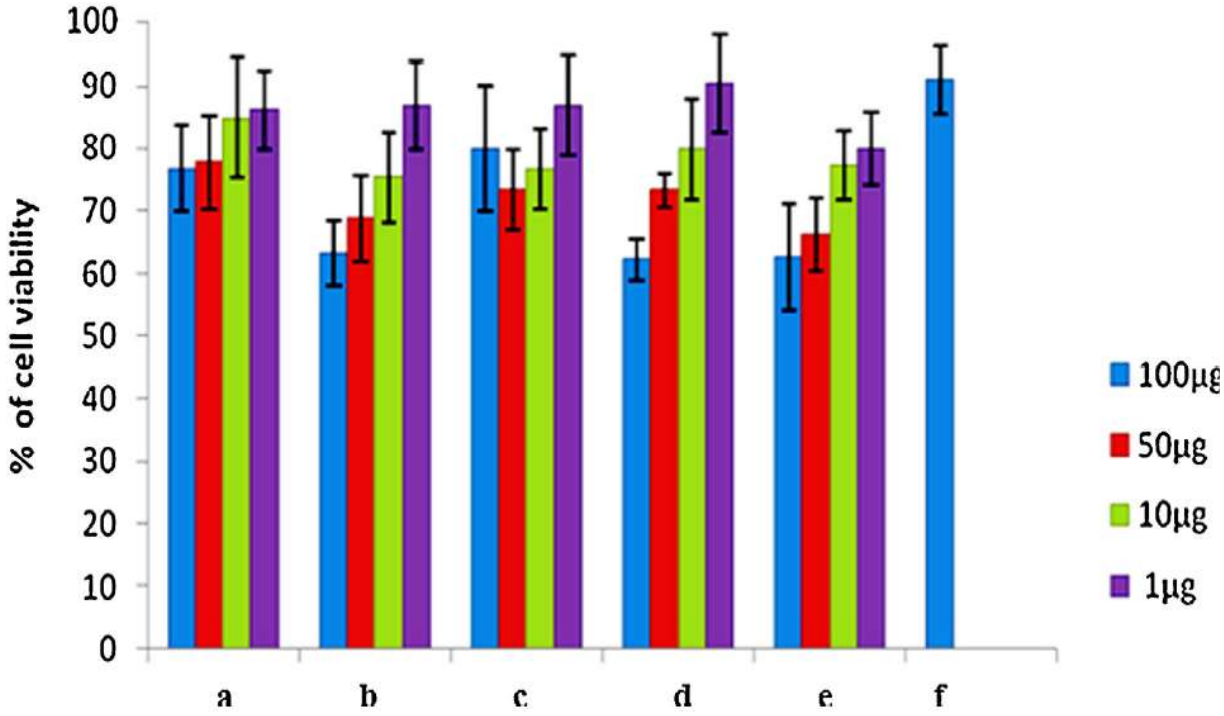


Fig. 4. Nanoparticle silver and gold biosynthesis: cytotoxic effects. (ref. No. 100)

5. Conclusion and summary

Creating a biosensor that can quickly and easily detect chemical and biological substances is crucial. Colorimetric assays based on Au NPs show promise since the whole assay can be conducted in a single solution containing the target and probes without washing stages. The color change may be seen immediately with the naked eye, eliminating the need for expensive equipment. As a result, the operational processes are greatly simplified, the detection times are shortened, and the assay costs are dramatically reduced using these methods. Furthermore, such colorimetric assays may be readily adapted to smartphone-based devices, which can be a robust platform for detecting, transducing, and analyzing real-time sensing data [102-104]. Using a smartphone-based approach is a fantastic strategy to advance colorimetric sensors.

Recent advancements in colorimetric techniques based on Au NPs, such as aggregation, etching, growth, and enzyme for sensing applications, were described in this overview. Many kinds of AuNP colorimetric tests have been presented, and some fascinating new approaches that provide excellent sensor performance have been explored. Nonetheless, a few significant problems will require fixing down the line. First, conventional Au NP-based systems are typically unable to detect biological and chemical targets at concentrations below the crucial threshold values, which is the case for many analytes, including tumor indicators and antibiotics.

Colorimetric strategies based on Au NPs have been integrated with other signal amplification techniques to increase sensitivity. On the downside, these amplification procedures often extend the detection time and add complexity to the experiment. One potential next step is to create ultrasensitive colorimetric sensors based on Au NPs that don't need amplification. Second, there has been a lot of interest in methods that allow for the simultaneous detection of numerous analytes in the same solution since doing so offers considerable advantages in speed, ease, and reagent use. Colorimetric sensors based on Au NPs have many applications and are easy to use, although they are often limited to single-target experiments. Because of developments in material science and analytical methods, a novel multicolor Au NPs sensor may be developed to detect many targets simultaneously.

While it's common knowledge that Au NPs may be manufactured on a large scale for use in colorimetric sensing applications, their potential in the industrial setting has not yet been investigated. There is a significant difference in the sensitivity and specificity of analyte tests in pure systems and complex samples. This may explain why many colorimetric assays based on

Au NPs are still at the proof-of-concept stage. In addition, the colored signal may be impacted by the color of the backdrop in actual sample solutions like human blood or industrial effluent.

References

[1] Grzelczak, M., Pérez-Juste, J., Mulvaney, P. and Liz-Marzán, L.M., 2008. Shape control in gold nanoparticle synthesis. *Chemical Society Reviews*, *37*(9), pp.1783-1791.

[2] de la Encarnación, C., de Aberasturi, D.J. and Liz-Marzán, L.M., 2022. Multifunctional plasmonic-magnetic nanoparticles for bioimaging and hyperthermia. *Advanced Drug Delivery Reviews*, p.114484.

[3] Glitscher, E.A., Bergueiro, J. and Calderón, M., 2022. Synthesis and anisotropic growth of glycerol-based thermoresponsive NIR plasmonic nanogels. *European Polymer Journal*, *175*, p.111342.

[4] Zhao, P., Li, N. and Astruc, D., 2013. State of the art in gold nanoparticle synthesis. *Coordination Chemistry Reviews*, *257*(3-4), pp.638-665.

[5] Firdhouse, M.J. and Lalitha, P., 2022. Biogenic Green Synthesis of Gold Nanoparticles and Their Applications–A Review of Promising Properties. *Inorganic Chemistry Communications*, p.109800.

[6] Doghish, A.S., Hashem, A.H., Shehabeldine, A.M., Sallam, A.A.M., El-Sayyad, G.S. and Salem, S.S., 2022. Nanocomposite based on gold nanoparticles and carboxymethyl cellulose: synthesis, characterization, antimicrobial, and anticancer activities. *Journal of Drug Delivery Science and Technology*, *77*, p.103874.

[7] Cheng, L., Wu, F., Tian, Y., Lv, X., Li, F., Xu, G., Hsu, H.Y., Zhang, Y. and Niu, W., 2023. Gap engineering of sandwich plasmonic gap nanostructures for boosting plasmon-enhanced electrocatalysis. *Nano Research*, pp.1-9.

[8] Turkevich, J., Stevenson, P.C. and Hillier, J., 1951. A study of the nucleation and growth processes in the synthesis of colloidal gold. *Discussions of the Faraday Society*, *11*, pp.55-75.

[9] Hidayah, A.N., Triyono, D., Herbani, Y. and Saleh, R., 2023. Tuning size and shape of gold nanoparticles using seed-mediated growth by unfocused femtosecond laser-induced plasma. *Optics Letters*, *48*(8), pp.2126-2129.

[10] Uniyal, S., Choudhary, K., Sachdev, S. and Kumar, S., 2022. Synthesis and characterization of gold nanoparticles and graphene oxide for the development of optical fiber biosensors. *Applied Optics*, *61*(26), pp.7618-7624.

[11] Li, M., Singh, R., Soares, M.S., Marques, C., Zhang, B. and Kumar, S., 2022. Convex fiber-tapered seven core fiber-convex fiber (CTC) structure-based biosensor for creatinine detection in aquaculture. *Optics Express*, *30*(8), pp.13898-13914.

[12] Zhang, G., Liu, Q., Xu, C. and Li, B., 2023. Uncovering Origin of Chirality of Gold Nanoparticles Prepared through the Conventional Citrate Reduction Method. *Analytical Chemistry*.

[13] Zhang, X., Wei, X., Qi, J., Shen, J., Xu, J., Gong, G., Wei, Y., Yang, J., Zhu, Q., Bai, T. and Guo, Z., 2022. Simultaneous detection of bladder cancer exosomal MicroRNAs based on inorganic nanoflare and DNAzyme walker. *Analytical Chemistry*, *94*(11), pp.4787-4793.

[14] Lin, S., Ze, H., Zhang, X.G., Zhang, Y.J., Song, J., Zhang, H., Zhong, H.L., Yang, Z.L., Yang, C., Li, J.F. and Zhu, Z., 2022. Direct and Simultaneous Identification of Multiple Mitochondrial Reactive Oxygen Species in Living Cells Using a SERS Borrowing Strategy. *Angewandte Chemie International Edition*, *61*(25), p.e202203511.

[15] Grubisic, A., Schweikhard, V., Baker, T.A. and Nesbitt, D.J., 2013. Coherent multiphoton photoelectron emission from single Au nanorods: The critical role of plasmonic electric near-field enhancement. *Acs Nano*, *7*(1), pp.87-99.

[16] Jiang, K., Wu, J., Kim, J.E., An, S., Nam, J.M., Peng, Y.K. and Lee, J.H., 2023. Plasmonic Cross-Linking Colorimetric PCR for Simple and Sensitive Nucleic Acid Detection. *Nano Letters*.

[17] Brust, M., Walker, M. and Bethell, D., 1994. Schiffrin DJ and Whyman R. *J. Chem. Soc. Chem. Commun.*, *1994*, p.801.

[18] Lindsey, J.S., Taniguchi, M., Bocian, D.F. and Holten, D., 2021. The fluorescence quantum yield parameter in Förster resonance energy transfer (FRET)—Meaning, misperception, and molecular design. *Chemical Physics Reviews*, *2*(1).

[19] Kolwas, K., Derkachova, A. and Shopa, M., 2009. Size characteristics of surface plasmons and their manifestation in scattering properties of metal particles. *Journal of Quantitative Spectroscopy and Radiative Transfer*, *110*(14-16), pp.1490-1501.

[20] Elghanian, R., Storhoff, J.J., Mucic, R.C., Letsinger, R.L. and Mirkin, C.A., 1997. Selective colorimetric detection of polynucleotides based on the distance-dependent optical properties of gold nanoparticles. *Science*, *277*(5329), pp.1078-1081.

[21] Satoh, H., Nakajima, M., Hirano, R. and Nakaya, Y., 2022. Highly sensitive and homogeneous detection of unamplified RNA based on the light scattering properties of gold nanoparticle probes. *Biosensors and Bioelectronics: X*, *12*, p.100249.

[22] Zhou, R., Li, Y., Dong, T., Tang, Y. and Li, F., 2020. A sequence-specific plasmonic loop-mediated isothermal amplification assay with orthogonal color readouts enabled by CRISPR Cas12a. *Chemical Communications*, *56*(24), pp.3536-3538.

[23] Xiao, L., Wei, L., He, Y. and Yeung, E.S., 2010. Single molecule biosensing using color coded plasmon resonant metal nanoparticles. *Analytical chemistry*, *82*(14), pp.6308-6314.

[24] Guo, Y., Tong, X., Ji, L., Wang, Z., Wang, H., Hu, J. and Pei, R., 2015. Visual detection of Ca 2+ based on aggregation-induced emission of Au (i)–Cys complexes with superb selectivity. *Chemical Communications*, *51*(3), pp.596-598.

[25] Jans, H. and Huo, Q., 2012. Gold nanoparticle-enabled biological and chemical detection and analysis. *Chemical Society Reviews*, *41*(7), pp.2849-2866.

[26] Zhang, S., Garcia-D'Angeli, A., Brennan, J.P. and Huo, Q., 2014. Predicting detection limits of enzyme-linked immunosorbent assay (ELISA) and bioanalytical techniques in general. *Analyst*, *139*(2), pp.439-445.

[27] Zhou, W., Gao, X., Liu, D. and Chen, X., 2015. Gold nanoparticles for in vitro diagnostics. *Chemical reviews*, *115*(19), pp.10575-10636.

[28] Saha, K., Agasti, S.S., Kim, C., Li, X. and Rotello, V.M., 2012. Gold nanoparticles in chemical and biological sensing. *Chemical reviews*, *112*(5), pp.2739-2779.

[29] Chen, J., Jiang, Z., Ackerman, J.D., Yazdani, M., Hou, S., Nugen, S.R. and Rotello, V.M., 2015. Electrochemical nanoparticle–enzyme sensors for screening bacterial contamination in drinking water. *Analyst*, *140*(15), pp.4991-4996.

[30] Elci, S.G., Yan, B., Kim, S.T., Saha, K., Jiang, Y., Klemmer, G.A., Moyano, D.F., Tonga, G.Y., Rotello, V.M. and Vachet, R.W., 2016. Quantitative imaging of 2 nm monolayer-protected gold nanoparticle distributions in tissues using laser ablation inductively-coupled plasma mass spectrometry (LA-ICP-MS). *Analyst*, *141*(8), pp.2418-2425.

[31] Saleh, S.M., Ali, R., Hirsch, T. and Wolfbeis, O.S., 2011. Detection of biotin–avidin affinity binding by exploiting a self-referenced system composed of upconverting luminescent nanoparticles and gold nanoparticles. *Journal of Nanoparticle Research*, *13*, pp.4603-4611.

[32] Ali, R., Alminderej, F.M. and Saleh, S.M., 2020. A simple, quantitative method for spectroscopic detection of metformin using gold nanoclusters. *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy*, *241*, p.118744.

[33] Saleh, S.M., Müller, R., Mader, H.S., Duerkop, A. and Wolfbeis, O.S., 2010. Novel multicolor fluorescently labeled silica nanoparticles for interface fluorescence resonance energy transfer to and from labeled avidin. *Analytical and bioanalytical chemistry*, *398*, pp.1615-1623.

[34] Aslan, K. and Pérez-Luna, V.H., 2002. Surface modification of colloidal gold by chemisorption of alkanethiols in the presence of a nonionic surfactant. *Langmuir*, *18*(16), pp.6059-6065.

[35] Aslan, K., Luhrs, C.C. and Pérez-Luna, V.H., 2004. Controlled and reversible aggregation of biotinylated gold nanoparticles with streptavidin. *The Journal of Physical Chemistry B*, *108*(40), pp.15631-15639.

[36] Chen, P., Chung, M.T., McHugh, W., Nidetz, R., Li, Y., Fu, J., Cornell, T.T., Shanley, T.P. and Kurabayashi, K., 2015. Multiplex serum cytokine immunoassay using nanoplasmonic biosensor microarrays. *ACS nano*, *9*(4), pp.4173-4181.

[37] Chen, J.S., Chen, P.F., Lin, H.T.H. and Huang, N.T., 2020. A Localized surface plasmon resonance (LSPR) sensor integrated automated microfluidic system for multiplex inflammatory biomarker detection. *Analyst*, *145*(23), pp.7654-7661.

[38] Bläsi, J. and Gerken, M., 2021. Multiplex optical biosensors based on multi-pinhole interferometry. *Biomedical optics express*, *12*(7), pp.4265-4275.

[39] Gao, Z., Song, Y., Hsiao, T.Y., He, J., Wang, C., Shen, J., MacLachlan, A., Dai, S., Singer, B.H., Kurabayashi, K. and Chen, P., 2021. Machine-learning-assisted microfluidic nanoplasmonic digital immunoassay for cytokine storm profiling in COVID-19 patients. *ACS nano*, *15*(11), pp.18023-18036.

[40] Flesch, J., Kappen, M., Drees, C., You, C. and Piehler, J., 2020. Self-assembly of robust gold nanoparticle monolayer architectures for quantitative protein interaction analysis by LSPR spectroscopy. *Analytical and Bioanalytical Chemistry*, *412*, pp.3413-3422.

[41] Philippi, M., Li, Z., Bhagawati, M. and You, C., 2021. Single Cell Pull-Down for Characterization of Protein Complexes. In *Handbook of Single-Cell Technologies* (pp. 563-584). Singapore: Springer Singapore.

[42] Chen, C.W., Zeng, X.Y., Cheng, C.C., Wang, C.F. and Chen, J.K., 2022. LSPR Sensing of Epithelial Cell Adhesion Molecules through Sphere and Cavity Plasmons of a Composite Ring Array of Poly [2-(dimethylamino) ethyl methacrylate]/Gold Nanoparticles. *Analytical Chemistry*.

[43] Ahn, H., Kim, S., Kim, Y., Kim, S., Choi, J.R. and Kim, K., 2021. Plasmonic sensing, imaging, and stimulation techniques for neuron studies. *Biosensors and Bioelectronics*, *182*, p.113150.

[44] Bhagawati, M., You, C. and Piehler, J., 2013. Quantitative real-time imaging of protein–protein interactions by LSPR detection with micropatterned gold nanoparticles. *Analytical chemistry*, *85*(20), pp.9564-9571.

[45] Flesch, J., Kappen, M., Drees, C., You, C. and Piehler, J., 2020. Self-assembly of robust gold nanoparticle monolayer architectures for quantitative protein interaction analysis by LSPR spectroscopy. *Analytical and Bioanalytical Chemistry*, *412*, pp.3413-3422.

[46] Ahn, H., Kim, S., Kim, Y., Kim, S., Choi, J.R. and Kim, K., 2021. Plasmonic sensing, imaging, and stimulation techniques for neuron studies. *Biosensors and Bioelectronics*, *182*, p.113150.

[47] Chen, C.W., Zeng, X.Y., Cheng, C.C., Wang, C.F. and Chen, J.K., 2022. LSPR Sensing of Epithelial Cell Adhesion Molecules through Sphere and Cavity Plasmons of a Composite Ring Array of Poly [2-(dimethylamino) ethyl methacrylate]/Gold Nanoparticles. *Analytical Chemistry*.

[48] Chen, S.J., Huang, Y.F., Huang, C.C., Lee, K.H., Lin, Z.H. and Chang, H.T., 2008. Colorimetric determination of urinary adenosine using aptamer-modified gold nanoparticles. *Biosensors and Bioelectronics*, *23*(11), pp.1749-1753.

[49] Huang, C.C., Huang, Y.F., Cao, Z., Tan, W. and Chang, H.T., 2005. Aptamer-modified gold nanoparticles for colorimetric determination of platelet-derived growth factors and their receptors. *Analytical chemistry*, *77*(17), pp.5735-5741.

[50] Chen, C.K., Huang, C.C. and Chang, H.T., 2010. Label-free colorimetric detection of picomolar thrombin in blood plasma using a gold nanoparticle-based assay. *Biosensors and Bioelectronics*, *25*(8), pp.1922-1927.

[51] Li, C.L., Huang, C.C., Chen, W.H., Chiang, C.K. and Chang, H.T., 2012. Peroxidase mimicking DNA–gold nanoparticles for fluorescence detection of the lead ions in blood. *Analyst*, *137*(22), pp.5222-5228.

[52] Chen, C.K., Shiang, Y.C., Huang, C.C. and Chang, H.T., 2011. Using self-assembled aptamers and fibrinogen-conjugated gold nanoparticles to detect DNA based on controlled thrombin activity. *Biosensors and Bioelectronics*, *26*(8), pp.3464-3468.

[53] Zhang, L., Zhao, J., Jiang, J. and Yu, R., 2012. Enzyme-regulated unmodified gold nanoparticle aggregation: a label free colorimetric assay for rapid and sensitive detection of adenosine deaminase activity and inhibition. *Chemical Communications*, *48*(89), pp.10996-10998.

[54] Gao, F., Du, L., Zhang, Y., Zhou, F. and Tang, D., 2016. A sensitive sandwich-type electrochemical aptasensor for thrombin detection based on platinum nanoparticles decorated carbon nanocages as signal labels. *Biosensors and Bioelectronics*, *86*, pp.185-193.

[55] Liu, D., Wang, Z., Jin, A., Huang, X., Sun, X., Wang, F., Yan, Q., Ge, S., Xia, N., Niu, G. and Liu, G., 2013. Back Cover: Acetylcholinesterase-Catalyzed Hydrolysis Allows Ultrasensitive Detection of Pathogens with the Naked Eye (Angew. Chem. Int. Ed. 52/2013). *Angewandte Chemie International Edition*, *52*(52), pp.14254-14254.

[56] Lin, J.H., Chang, C.W., Wu, Z.H. and Tseng, W.L., 2010. Colorimetric assay for S-adenosylhomocysteine hydrolase activity and inhibition using fluorosurfactant-capped gold nanoparticles. *Analytical chemistry*, *82*(21), pp.8775-8779.

[57] Yang, Y.C. and Tseng, W.L., 2016. 1, 4-Benzenediboronic-acid-induced aggregation of gold nanoparticles: application to hydrogen peroxide detection and biotin–avidin-mediated immunoassay with naked-eye detection. *Analytical chemistry*, *88*(10), pp.5355-5362.

[58] Ou, L.J., Jin, P.Y., Chu, X., Jiang, J.H. and Yu, R.Q., 2010. Sensitive and visual detection of sequence-specific DNA-binding protein via a gold nanoparticle-based colorimetric biosensor. *Analytical Chemistry*, *82*(14), pp.6015-6024.

[59] Chen, Z., Zhang, Z., Qu, C., Pan, D. and Chen, L., 2012. Highly sensitive label-free colorimetric sensing of nitrite based on etching of gold nanorods. *Analyst*, *137*(22), pp.5197-5200.

[60] Yu, K.X., Qiao, Z.J., Song, W.L. and Bi, S., 2021. DNA nanotechnology for multimodal synergistic theranostics. *Journal of Analysis and Testing*, *5*(2), pp.112-129.

[61] Aroua, L.M., Ali, R., Albadri, A.E., Messaoudi, S., Alminderej, F.M. and Saleh, S.M., 2023. A New, Extremely Sensitive, Turn-Off Optical Sensor Utilizing Schiff Base for Fast Detection of Cu (II). *Biosensors*, *13*(3), p.359.

[62] Ali, R., Ghannay, S., Messaoudi, S., Alminderej, F.M., Aouadi, K. and Saleh, S.M., 2022. A Reversible Optical Sensor Film for Mercury Ions Discrimination Based on Isoxazolidine Derivative and Exhibiting pH Sensing. *Biosensors*, *12*(11), p.1028.

[63] Saleh, S.M., El-Sayed, W.A., El-Manawaty, M.A., Gassoumi, M. and Ali, R., 2022. Microwave-Assisted Rapid Synthesis of Luminescent Tryptophan-Stabilized Silver Nanoclusters for Ultra-Sensitive Detection of Fe (III), and Their Application in a Test Strip. *Biosensors*, *12*(6), p.425.

[64] Saleh, S.M., El-Sayed, W.A., El-Manawaty, M.A., Gassoumi, M. and Ali, R., 2022. An eco-friendly synthetic approach for copper nanoclusters and their potential in lead ions sensing and biological applications. *Biosensors*, *12*(4), p.197.

[65] Ali, R., Ali, I.A., Messaoudi, S., Alminderej, F.M. and Saleh, S.M., 2021. An effective optical chemosensor film for selective detection of mercury ions. *Journal of Molecular Liquids*, *336*, p.116122.

[66] Saleh, S.M., Alminderej, F.M., Ali, R. and Abdallah, O.I., 2020. Optical sensor film for metribuzin pesticide detection. *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy*, *229*, p.117971.

[67] Saleh, S.M., Ali, R., Hegazy, M.E.F., Alminderej, F.M. and Mohamed, T.A., 2020. The natural compound chrysosplenol-D is a novel, ultrasensitive optical sensor for detection of Cu (II). *Journal of Molecular Liquids*, *302*, p.112558.

[68] Ali, R., Alminderej, F.M., Messaoudi, S. and Saleh, S.M., 2021. Ratiometric ultrasensitive optical chemisensor film based antibiotic drug for Al (III) and Cu (II) detection. *Talanta*, *221*, p.121412.

[69] Saleh, S.M., Ali, R., Alminderej, F. and Ali, I.A., 2019. Ultrasensitive optical chemosensor for Cu (II) detection. *International journal of analytical chemistry*, *2019*.

[70] Ali, R., Saleh, S.M. and Aly, S.M., 2017. Fluorescent gold nanoclusters as pH sensors for the pH 5 to 9 range and for imaging of blood cell pH values. *Microchimica Acta*, *184*, pp.3309-3315.

[71] Saleh, S.M., Almotiri, M.K. and Ali, R., 2022. Green synthesis of highly luminescent gold nanoclusters and their application in sensing Cu (II) and Hg (II). *Journal of Photochemistry and Photobiology A: Chemistry*, *426*, p.113719.

[72] Ali, R., Alfeneekh, B., Chigurupati, S. and Saleh, S.M., 2022. Green synthesis of pregabalin-stabilized gold nanoclusters and their applications in sensing and drug release. *Archiv der Pharmazie*, *355*(4), p.2100426.

[73] Saleh, S.M., Ali, R., Hirsch, T. and Wolfbeis, O.S., 2011. Optical detection of biotin-avidin affinity binding by exploiting a self-referenced system composed of upconverting nanoparticles and gold nanoparticles. *J Nanoparticle Res. doi*, *10*.

[74] You, C.C., Miranda, O.R., Gider, B., Ghosh, P.S., Kim, I.B., Erdogan, B., Krovi, S.A., Bunz, U.H. and Rotello, V.M., 2007. Detection and identification of proteins using nanoparticle–fluorescent polymer 'chemical nose'sensors. *Nature nanotechnology*, *2*(5), pp.318-323.

[75] Yeo, E.L.L., Cheah, J.U.J., Thong, P.S.P., Soo, K.C. and Kah, J.C.Y., 2019. Gold nanorods coated with apolipoprotein E protein corona for drug delivery. *ACS Applied Nano Materials*, *2*(10), pp.6220-6229.

[76] Nejati, K., Dadashpour, M., Gharibi, T., Mellatyar, H. and Akbarzadeh, A., 2021. Biomedical applications of functionalized gold nanoparticles: a review. *Journal of Cluster Science*, pp.1-16.

[77] Saleh, S.M., Elkady, E.M., Ali, R., Alminderej, F. and Mohamed, T.A., 2018. Novel chemical sensor for detection Ca (II) ions based on ferutinin. *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy*, *205*, pp.264-268.

[78] Narang, J., Malhotra, N., Singh, G. and Pundir, C.S., 2015. Electrochemical impediometric detection of anti-HIV drug taking gold nanorods as a sensing interface. *Biosensors and Bioelectronics*, *66*, pp.332-337.

[79] Murphy, C.J., Thompson, L.B., Alkilany, A.M., Sisco, P.N., Boulos, S.P., Sivapalan, S.T., Yang, J.A., Chernak, D.J. and Huang, J., 2010. The many faces of gold nanorods. *The Journal of Physical Chemistry Letters*, *1*(19), pp.2867-2875.

[80] Burrows, N.D., Harvey, S., Idesis, F.A. and Murphy, C.J., 2017. Understanding the seed-mediated growth of gold nanorods through a fractional factorial design of experiments. *Langmuir*, *33*(8), pp.1891-1907.

[81] Ali, M.R., Ali, H.R., Rankin, C.R. and El-Sayed, M.A., 2016. Targeting heat shock protein 70 using gold nanorods enhances cancer cell apoptosis in low dose plasmonic photothermal therapy. *Biomaterials*, *102*, pp.1-8.

[82] Ali, M.R., Rahman, M.A., Wu, Y., Han, T., Peng, X., Mackey, M.A., Wang, D., Shin, H.J., Chen, Z.G., Xiao, H. and Wu, R., 2017. Efficacy, long-term toxicity, and mechanistic studies of gold nanorods photothermal therapy of cancer in xenograft mice. *Proceedings of the National Academy of Sciences*, *114*(15), pp.E3110-E3118.

[83] Wang, S., Ding, Y., Wang, H., Li, W., Xu, W., Sun, P., Huang, W., Chen, Y., Gu, J., Lin, P. and Ma, L., 2022. Molecularly imprinted upconversion nanoparticles for active tumor targeting and microinvasive photothermal therapy. *Journal of Materials Science*, *57*(8), pp.5177-5197.

[84] Liu, Y., Ma, W. and Wang, J., 2018. Theranostics of gold nanoparticles with an emphasis on photoacoustic imaging and photothermal therapy. *Current Pharmaceutical Design*, *24*(23), pp.2719-2728.

[85] Liu, Y., Ma, W. and Wang, J., 2018. Theranostics of gold nanoparticles with an emphasis on photoacoustic imaging and photothermal therapy. *Current Pharmaceutical Design*, *24*(23), pp.2719-2728.

[86] Yang, Z., Sun, Z., Ren, Y., Chen, X., Zhang, W., Zhu, X., Mao, Z., Shen, J. and Nie, S., 2019. Advances in nanomaterials for use in photothermal and photodynamic therapeutics. *Molecular medicine reports*, *20*(1), pp.5-15.

[87] Hu, Y., Huang, S., Zhao, X., Chang, L., Ren, X., Mei, X. and Chen, Z., 2021. Preparation of photothermal responsive and ROS generative gold nanocages for cancer therapy. *Chemical Engineering Journal*, *421*, p.129744.

[88] Pakravan, A., Azizi, M., Rahimi, F., Bani, F., Mahmoudzadeh, F., Salehi, R. and Mahkam, M., 2021. Comparative effect of thermo/pH-responsive polymer-coated gold nanocages and

hollow nanostars on chemo-photothermal therapy of breast cancer cells. *Cancer Nanotechnology*, *12*(1), pp.1-26.

[89] Elahi, N., Kamali, M. and Baghersad, M.H., 2018. Recent biomedical applications of gold nanoparticles: A review. *Talanta*, *184*, pp.537-556.

[90] Rabiee, N., Bagherzadeh, M., Ghasemi, A., Zare, H., Ahmadi, S., Fatahi, Y., Dinarvand, R., Rabiee, M., Ramakrishna, S., Shokouhimehr, M. and Varma, R.S., 2020. Point-of-use rapid detection of SARS-CoV-2: nanotechnology-enabled solutions for the COVID-19 pandemic. *International journal of molecular sciences*, *21*(14), p.5126.

[91] Love, A.J. and Taliansky, M.E., 2018. Propagation and isolation of tobacco mosaic virus that surface displays metal binding and reducing peptides for generation of gold nanoparticles. *Virus-Derived Nanoparticles for Advanced Technologies: Methods and Protocols*, pp.363-381.

[92] Kurgan, N. and Karbivskyy, V., 2020. Properties of nanowires based on the tobacco mosaic virus and gold nanoparticles. *Applied Nanoscience*, *10*, pp.2685-2689.

[93] Huang, X., Chang, L., Lu, Y., Li, Z., Kang, Z., Zhang, X., Liu, M. and Yang, D.P., 2020. Plant-mediated synthesis of dual-functional Eggshell/Ag nanocomposites towards catalysis and antibacterial applications. Materials Science and Engineering: C, 113, p.111015.

[94] Huo, C., Khoshnamvand, M., Liu, P., Liu, C. and Yuan, C.G., 2019. Rapid mediated biosynthesis and quantification of AuNPs using persimmon (Diospyros Kaki Lf) fruit extract. *Journal of Molecular Structure*, *1178*, pp.366-374.

[95] Duan, F., Hu, M., Guo, C., Song, Y., Wang, M., He, L., Zhang, Z., Pettinari, R. and Zhou, L., 2020. Chromium-based metal-organic framework embedded with cobalt phthalocyanine for the sensitively impedimetric cytosensing of colorectal cancer (CT26) cells and cell imaging. *Chemical Engineering Journal*, *398*, p.125452.

[96] Zhou, Z., Liu, M. and Jiang, J., 2018. The potential of aptamers for cancer research. *Analytical biochemistry*, *549*, pp.91-95.

[97] Elahi, N., Kamali, M. and Baghersad, M.H., 2018. Recent biomedical applications of gold nanoparticles: A review. *Talanta*, *184*, pp.537-556.

[98] Ma, X., Kou, X., Xu, Y., Yang, D. and Miao, P., 2019. Colorimetric sensing strategy for heparin assay based on PDDA-induced aggregation of gold nanoparticles. *Nanoscale Advances*, *1*(2), pp.486-489.

[99] Qin, L., Niu, D., Jiang, Y., He, J., Jia, X., Zhao, W., Li, P. and Li, Y., 2019. Confined growth of multiple gold nanorices in dual-mesoporous silica nanospheres for improved computed tomography imaging and photothermal therapy. *International journal of nanomedicine*, *14*, p.1519.

[100] Krishnaraj, C., Muthukumaran, P., Ramachandran, R., Balakumaran, M.D. and Kalaichelvan, P.T., 2014. Acalypha indica Linn: biogenic synthesis of silver and gold nanoparticles and their cytotoxic effects against MDA-MB-231, human breast cancer cells. *Biotechnology Reports*, *4*, pp.42-49.

[101] Kalimuthu, K., Cha, B.S., Kim, S. and Park, K.S., 2020. Eco-friendly synthesis and biomedical applications of gold nanoparticles: A review. *Microchemical Journal*, *152*, p.104296.

[102] Kim, H.S. and Lee, D.Y., 2018. Near-infrared-responsive cancer photothermal and photodynamic therapy using gold nanoparticles. *Polymers*, *10*(9), p.961.

[103] Youssef, Z., Yesmurzayeva, N., Larue, L., Jouan-Hureaux, V., Colombeau, L., Arnoux, P., Acherar, S., Vanderesse, R. and Frochot, C., 2019. New targeted gold nanorods for the treatment of glioblastoma by photodynamic therapy. *Journal of Clinical Medicine*, *8*(12), p.2205.

[104] Nagy-Simon, T., Potara, M., Craciun, A.M., Licarete, E. and Astilean, S., 2018. IR780-dye loaded gold nanoparticles as new near infrared activatable nanotheranostic agents for simultaneous photodynamic and photothermal therapy and intracellular tracking by surface enhanced resonant Raman scattering imaging. *Journal of colloid and interface science*, *517*, pp.239-250.