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REVIEW

Gold Nanoparticles for Targeting of Biomedical Applications

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The advancement of techniques for synthesizing nanoparticles is an important step in the field of nanotechnology. Gold nanoparticles (AuNPs) are increasing popular for detection of a multitude of biomolecules, proteins and nucleic acids. Incorporating AuNPs onto the sensing surface of biosensors to identify molecules with improved signals has been the subject of extensive research in the past ten years. This brief review describes the methods of AuNPs synthesis and their applications. It also describes a recent method to enhance surface plasmon resonance (SPR) detection capabilities using AuNPs.

Keywords: Cancer, Gold nanoparticles, Biomedical applications.

INTRODUCTION

Nanoparticles with the size of around 100 nm have some different physical, chemical and biological properties in comparison with the bulk ones. The differences in properties mainly lie in the physical structure of atoms, molecules of the elements, which caused the different in physico-chemical properties [1-3]. Another benefit of nanoparticles is their large surface area to volume ratio, leading to carry abundant amount of target molecules for drug delivery. Nowadays, a large number of nanoparticles have been developed with unique properties, leading to wide range of applications and opening opportunities for several activities [4-8].

A lot types of nanoparticles including polymeric nanoparticles [9,10], liposomes [11,12], carbon dots [13,14], upconverting nanoparticles and inorganic nanoparticles have been developed for drug delivery. Inorganic nanoparticles include silver, silica, gold, quantum dots and iron oxide nanoparticles [15-20]. All of these nanoparticles have their benefits. However, gold nanoparticles (AuNPs) have received enormous attention of the researchers due to their chemically inert and minimally toxic, leading to believe that they can pass through as ideal drug delivery [21,22].

In recent past, many researches have been focused on synthesis of AuNPs. The size and shape of AuNPs, which can be selected under various experimental conditions for the desired purpose. The different shapes of AuNPs can be verified such as nanostars, nanorods, nanosquares [23-25]. Here, the synthesis process of AuNPs performed based on the reduction of Au(III) to Au(0). Small seeds of AuNPs are generated, generally 3-4 nm in size and the addition of these seeds to Au(III) solution containing various reducing and capping agents can be effected the shape of the nucleated nanomaterials [26]. AuNPs have been synthesized based on physico-chemical techniques including chemical reduction [27], γ-ray radiation [28], micro emulsion [29], electrochemical method [30], laser ablation [31], autoclave [32], microwave [33] and photochemical reduction [34]. These synthesized process have effective benefits, however, they are associated with the inherent drawbacks liked high operational cost, use of toxic agents. To overcome those limitations, new alternative for AuNPs synthesis based on green method are emerging rapidly [35-37]. For the biological applications, the surface of AuNPs is easily functionalized with chemical grosslinker to enhance surface absorption liked gold-sulfure (Au-S) bonds [38-40], gold-polyethylene glycol (PEG) ligands [41,42].

In this review article, the biomedical applications *i.e.* drug delivery relying on AuNPs. Various processes on the basis of immune reaction for specific detection such as glucose functionalized AuNPs, T antigen bound AuNPs or polylysin chain

conjugation AuNPs for cancer treatment are described with the relevant surface chemistry accessible to the AuNPs surface.

Gold nanoparticle synthesis: Nanoparticles can be fabricated by two different methods *i.e.* the "top-down" and the "bottom-up" approach as shown in Fig. 1. In the top-down approach, the AuPNs were produced by taking place from the macro-sized materials. The bulk materials was split into tiny particles by reduction of size utilizing with various techniques *i.e.*, pulsed laser ablation, ball milling, lithography and pules wire discharge [43-46]. However, these techniques have inherent drawbacks such as requiring a substantial space, needing a lot of energy for the source and entailing a lot of time. Moreover, one of the important limitation in this technique is the defects in the surface structure of the nanoparticles, which was affected to the important physical properties liked surface to volume ratio [47-49].

In bottom up approach, this is more common method. The AuNPs were created based on atoms based on different chemical methods liked chemical reduction [50], electrochemical [51], sonochemical [52], microemulsion [53] and pyrolysis [54]. There are many advantages based on these methods are that the AuNPs can be synthesized with large amount in short period, cost-effective and easily scaled up [55,56].

Characterization of gold nanoparticles: In order to gain insight about the physical properties, size, crystal structure, elemental composition and form of AuNPs, as well as to explore their specific size and shape, characterization was carried out. Basically, the surface topography, particle size and surface are investigated by scanning electron microscopy (SEM), transmission electron microscopy (TEM) and atomic force microscopy (AFM). Both of them scans the AuNPs surface with high energy electron beam [57]. The crystal structure, the crystalline conformation of oxidation and composition of AuNPs can be studied based on X-ray diffraction (XRD) [58]. The scattering and absorption properties of AuNPs can be measured based on UV-visible spectroscopy [59]. To verify the chemical bonds presented in the AuNPs surface, the absorption peaks that related to bond variation was studied utilizing the Fourier transform infrared spectroscopy. In addition, the electric charges presented on the AuNPs were investigated based on zeta potential device. Normally, the zeta potential value of around – 10 mV to + 10 mV were said to be neutral. However, this value is larger than + 30 nm, this is cationic materials in nature. Otherwise, this value is smaller than – 30 nm, this is anionic materials in nature [60].

Application and mechanism of gold nanoparticles: Recent studies have demonstrated that the unique features of AuNPs make them suitable for targeted drug delivery. Consequently, these applications are discussed in the following sections.

One of the important applications for medication is drug delivery for cancers treatment utilizing antibody directed AuNPs. Antibodies were highly specific towards a receptor that display a high affinity. For example, Goddard *et al.* [61] represented that the modified peptide to allow for specific conjugation onto PEG ligands. They demonstrated that these peptide–C11Pc–PEG–AuNPs produced singlet oxygen upon irradiation at wavelength of 633 nm. These nanosystems demonstrated high effectiveness in inhibiting EGFR overexpression in A549 cells using 4 nM AuNPs, resulting in only 7% cell viability after irradiation and minimal toxicity in the absence of light [61]. In addition, Cabezón *et al.* [62] stated that transcytosis has been extensively employed as a potential method for transporting neurotherapeutics across the blood-brain barrier. The findings revealed that the majority of vesicles undergo intracellular processes including fusion and rearrangement, resulting in the accumulation of AuNPs in late multivesicular structures that contain a significant amount of AuNPs. In 2010, Masereel *et al*. [63] conducted research on cancer treatment and imaging using AuNPs, which presents a straightforward and dependable liquid technique for sequentially coating gold nanoparticles (diameter: 21 nm) with alternating layers of cationic polyallylamine and anionic polystyrenesulfonate. The C-terminal amino acid of the antibody targeting anti-bovine serum albumin was activated using EDC/NHS and subsequently combined with the amino groups of the exterior polyallylamine layer. In order to investigate the behaviour of a colloidal solution containing 10^5-10^{13} virions/mL, Minopoli *et al*. [64] introduced functionalized gold nanoparticles (f-AuNPs) and simulated SARS-CoV-2 virions. The results also demonstrate that the virions must be kept at a close distance (~ 5 nm) from the f-AuNP in order to prevent the hook effect. This highlights the need for an appropriate functionalization method that maintains a thin dielectric layer (*e.g.* proteins or aptamers) around the AuNPs. The potential for diagnostic testing to be advanced by focusing on the distinctive characteristics of AuNPs was demonstrated by Ruiz *et al.* [65]. The immobilization of antibodies onto the surface of AuNPs allows for selective binding to target species and is fundamental to many of these nanoparticle enabled approaches. This work investigated the effect of protein charge on adsorption to AuNPs by systematically controlling the surface

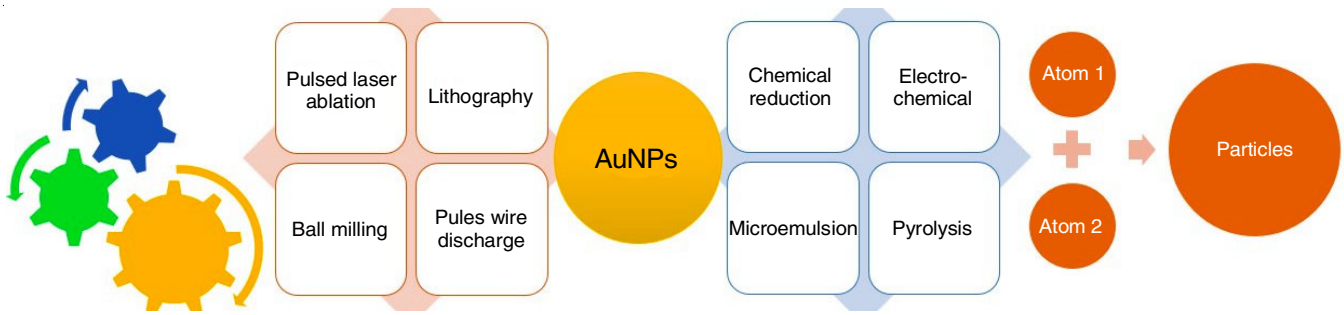

Fig. 1. Schematic diagram for synthesis of AuNPs

charge distribution on an antibody using pH. The Hill-modified Langmuir equation was used to obtain the adsorption affinity, protein layer thickness, and binding cooperativity at each pH from the adsorption isotherms. There was no change in the anti-HRP-AuNP binding constants within the pH range of 7.5-8.5, when a monolayer of antibody is generated at satu-ration. Zhu *et al*. [66] demonstrated that due to their capacity to irreversibly bind to biomolecules, including DNA, AuNPs smaller than 2 nm are more likely to cause toxicity, while AuNPs larger than 3 nm are generally considered to be harmless. The findings of this study shown that 20 nm AuNPs have a wide range of biodistribution, which exposes more organs to AuNPs, particularly the spleen and liver.

For targeted biofunctionalization, Tort *et al*. [67] demonstrated the utilization of oligonucleotide encoded AuNPs directed immobilization on a DNA microarray. Findings from the preliminary study suggest that the detectability achieved can be comparable to other immunochemical detection systems that use labels or amplification techniques, for example, immobilizing sets of nanoparticles that vary in shape or material. This opens the possibility of creating chips with a dual identification mode. Using a new tumor targeting antibody that targets colon expressing FAT1, Cordiali-Fei *et al*. [68] showed the efficacy of Au NPs delivery. Researchers have shown that negatively charged AuCOOH mAB198.3 particles have a larger effect on intracellular uptake in both laboratory and living organism bioimaging investigations, suggesting that this compound may have uses in cancer treatment. Conjugated AuNPs with tumor-targeting moieties attach specifically and strongly to cancer cells as reported by Li *et al*. [69]. In addition, when exposed to ionizing radiations such as proton ions, they enhance cell death. The discovery has implications for the development of targeted cancer nanotherapy and treatment planning with the goal of improving proton ion therapies and, in the end, lowering radiation damage to healthy tissues surrounding the tumor. Table-1 briefly illustrated the details of the various AuNPs based biosensors with their size and specific targets of cancer cells. However, there is still a long way to go before this technique is considered safe.

TABLE-1
TARGETING MOIETY AND TYPE OF CANCER TREATED BY AuNPs

AuNPs morphology	Cancer type	Biological target	Ref.
14 nm, spherical	Breast	Protein	[70]
50 nm, spherical	Skin	A431 skin cancer cells	[71]
20 nm, spherical	Bladder	Cancer 5637 cells	[72]
20 nm, spherical	Head	Tau phosphorylation	[73]
5 nm, spherical	Neck	Carcinoma cell line HSC-3	[74]
13.6 nm, spherical	Lung	A549, H460 and H520 cells	[75]
50 nm, spherical	Colon	HCT-116 cells	[76]
30 nm, spherical	Liver	HepG2 cells	[77]

An innovative magnetic biosensor for the detection of antibodies anti-hepatitis B surface antigen (1-HBsAg) in human serum was introduced by Muniz *et al*. [78] using AuNPs labels. In human serum, the created biosensor can detect 1-HBsAg IgG antibodies at concentrations as low as 3 mIU/mL, and it is sensitive enough to ensure detection at concentrations as high as 10 mIU/mL, the minimum threshold for HBsAg responders. Since it is quicker, easier, and cheaper than the conventional approaches, this biosensor can be used to detect 1-HBsAg IgG antibodies in human serum. The GBP-ProA proteins were effectively mounted onto SPR chips using the GBP domain, Ko *et al*. [79] demonstrated that the ProA part of the layered GBP-ProA allowed for simple and oriented antibody binding without the need for additional chemical treatment. Another advantage of biomolecular interaction signals was the direct assembly of AuNPs onto SPR chip surfaces. There was a 10-folds increase in sensitivity for *S. typhimurium* detection when using the AuNPs assembled chip as opposed to the bare chip, thanks to the signal augmentation. Špringer & Homola [80] introduced the utilization of novel bioAuNPs that have been enhanced to have improved binding and non-fouling characteristics. They also provided evidence of the effectiveness of these bioAuNPs in detecting carcinoembryonic antigen in human blood plasma, specifically in a 50% concentration. The utilization of bio-AuNPs enhanced the detection limit by over 1,000 times compared to previously published results. Wang *et al*. [81] developed a biosensor for the detection of microRNA (miRNA) using surface plasmon resonance (SPR) and gold nanoparticles (AuNPs) combined with DNA supersandwich. When the target is present, the stem-loop structure of the capture DNA on the Au film surface is unfolded and DNA-linked AuNPs are attached to the Au film by hybridizing with the end of the capture DNA. Subsequently, the helper DNA attached to the AuNPs can initiate an alternate hybridization process using two report probes, leading to the formation of a DNA supersandwich. The resonance angle shift was significantly amplified due to the electrical connection between the localized plasmon of AuNPs and the surface plasmon wave associated with the Au film, as well as the increased refractive index of the medium adjacent to the metal film generated by the DNA supersandwich structure. In order to detect doxycycline, Kazmi *et al*. [82] demonstrated an ultrasensitive SPR biosensor based on doxy-AuNPs. The biosensor response changed as a function of doxy-AuNPs size and development rate. The low molecular weight of the analyte was not an obstacle when doxy-AuNPs (100 mMNaCl) were used as an amplification element to achieve a much improved SPR response. As an alternative to traditional methods for doxycycline detection, this SPR biosensor (as low as 7 pM) is highly effective due to its high sensitivity, low limit of detection, great signal response time (> 0.5 h), superior stability and repeatability. A sensitive and adaptable SPR biosensor based on GO-AuNPs composites was reported by Li *et al*. [83] based on two-layered configuration of GO-AuNPs in order to improve the signal. A higher SPR response was achieved because the funct-ionalized Au film at the bottom of the stack had a large specific surface area, allowing it to immobilize more attract DNA mole-cules. An even stronger SPR response was possible because to the top layers signal-enhancing label. Moreover, it was also possible to successfully use the SPR biosensor in complicated systems like cancer cell extraction, serum and exhibit a reason-able selectivity. A miRNA-detecting sensitive SPR biosensor

TABLE-2
SPR BIOSENSORS INCORPORATING GOLD NANOPARTICLES

AuNPs morphology	Detection limit	Features	Ref.
4 nm, spherical	0.1 pg mm^2	AuNPs incorporated in SiO_2 film	[85]
4 nm, spherical	2×10^{-13} M	AuNPs embedded in polymer	[86]
10 nm, spherical	0.05 µg mL^{-1}	Compares direct and sandwich assays	[87]
40 nm, nanorods	10^{-18} M	Sandwich assay based on Au nanorods	[88]
13 nm, spherical	8.6 pg mL^{-1}	AuNP labeling binding on the surface	[89]
5 nm, spherical	0.1 ng mL^{-1}	Silica spacing layer	[90]
10 nm, spherical	8.6 pp mL^{-1}	Competitive inhibition assay	[91]
10 nm, spherical	8.6 pp mL^{-1}	Sandwich immunoassay	[92]

utilizing AuNPs-MoS2 nanocomposites was introduced by Nie *et al*. [84]. The AuNPs/MoS_2-SPR biosensor showed a high sensitivity toward target miRNA with a detection limit of 0.5 fM, which was based on the signal amplification of AuNPs-MoS_2 nanocomposites. Human miRNA from cancer cells could be monitored using the developed biosensor, which exhibited good specificity, acceptable repeatability and accuracy. The results from the qRT-PCR assay were consistent with those from the AuNPs/MoS_2-SPR biosensor. Furthermore, it may be possible to determine miRNA in 10% normal human serum using the method that was provided. The assay was both economical and enzyme-free, which is of utmost importance. These unique characteristics suggest that this approach has great potential as a miRNA detection test for use in clinical diagnosis and illness treatment.

The most significant enhancements in sensitivity observed in SPR sensing technologies occur when gold nanoparticles (AuNPs) are utilized as labels. The sensor sensitivity can enhance the range by a factor of 4 to several hundred times when compared to unamplified techniques. The shift in SPR signal occurs because of alterations in the dielectric medium near the surface. The presence of extra dosage of AuNPs also contributes to the variations in SPR signal. The enhancements in sensitivity have been exhibited for various analytes as shown in Table-2.

Conclusion and future prospects

The sensitivity of SPR biosensors can be enhanced based on the technique using gold nanoparticles. Besides, the label-free detection of surface plasmon resonance (SPR) biosensors has desirable applications, thus label-free detection method involving gold nanoparticles (AuNPs) incorporating are interesting. The special characteristic features and properties of AuNPs can be applied in various field of applications *i.e.* targeted drug delivery, nano-electronics, biosensors, gene delivery, *etc*. There is a space for future exploration into the areas of AuNPs immobilization on SPR sensing surface. The deeper knowledge of green chemistry as a promising method of synthesis AuNPs in the upcoming future may open up new possibilities and develop promising applications of AuNPs. In addition, the continuous development in the field of SPR biosensor has paved a new area of AuNPs for the development of diagnostic purposes. The AuNPs enhanced sandwich assays have been shown to be benefit to apply for improving of sensor detection limit and sensor sensitivity. Moreover, SPR imaging combined with microarrays and particle-enhanced sensitivity methods could be a promising technique for high throughput applications. The use of AuNPs in these biosensors appears to be a future trend for further research.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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