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Review on Gold Nanoparticles and Their Applications as Smart Sensing Devices

Muhammad Syadzwan Fuad Hilmi[1,a], Syaza Azhari[1,b], Mohd Hafiz Abu Hassan[1,c]

[1]*Faculty of Science and Technology, Universiti Sains Islam Malaysia (USIM), Bandar Baru Nilai, 71800 Nilai, Negeri Sembilan, Malaysia*

E-mail: [a]muhammadsyadzwan.fst@gmail.com, [b]syaza@usim.edu.my, [c]mhafiz.a.h@usim.edu.my

***Abstract*— Gold nanoparticles (GNPs) are attractive materials that are widely used in many fields due to the unique optical, physical and chemical properties. Recently, many advancements were made in biomedical applications as a smart sensing device with better biocompatibility in disease diagnosis. GNPs could be prepared and conjugated with many functionalizing thorough chemical and biosynthesis. Qualitative analysis on several related articles manage to investigate the synthesis of gold nanoparticles, including surface functionalization with a wide range of molecules to improve the applications of gold nanoparticles in targeting drugs in various cancers, gene therapy and other diseases.**

***Keywords*— Gold nanoparticles; Sensing devices.**

I. INTRODUCTION

Recently, there are many studies which use the gold nanoparticles (AuNPs) for detection of ions or small molecule, nucleic acids (including DNA and RNA), and protein [1]-[6]. AuNPs have interesting optical properties including the high surface area to volume ratio, which contribute to high sensitivity and selectivity for detection. AuNPs can exist in many shapes like nanospheres, hollow spheres, nanorods and nanorings by changing the optical or electrical properties. Moreover, the optical properties of AuNPs significantly determined on its morphology and physiology characteristics, i.e., on its size, shape, and accumulation state, which can be altered by selecting the suitable synthesis and stabilization agent [7]. Basically, colloid gold exists in red or pink colour, but can be changed to purple-blue colour by aggregation, where the AuNPs surface bind with targeting analyte, which causes to change in colour [3].

Various techniques to synthesis AuNPS have been discovered by other researchers and these techniques are divided into two principles, which are top down and bottom up methods [8]. The top down method is the method where some matter is removed from bulk material to get the nanostructure. While bottom up method is the most popular way to synthesis AuNPs where the atom is assembled into a nanostructure. The most common bottom up method is Turkervich method which was first developed in 1951. Basically, the Turkervich method is the reduction of gold chloride to gold atom by using a stabilizing agent [9].

In particular, gold nanoparticles (AuNPs) based sensors has been a great research interest that demonstrated great utility in chemical and biomedical detection because of their unique optical and electrical properties. The high surface to volume ratio and fascinating optical properties of AuNPs assists highly sensitive and selective detection. Since AuNPs have very high stability in their environment, they exhibit colour change that can be easily detected by the naked eye without the analysis using any instrument. AuNPs that become stable by addition of citrate permit red in solution and can be seen at low concentration [10]. While the addition of a destabilizing or a binding molecule give the AuNPs a "blue shift" in the UV-Visible spectra and in certain cases to aggregate into a purple solution when they are destabilized. This forms the basis of colorimetric detection, wherein binding the target analyte to GNP surface results in aggregation ultimately leading to change in colour, concomitant with broadening and shifting of the peak [6], [11].

AuNPs are considered as one of the most convenient carrier systems that is applicable in various medical related research fields, including bio sensing and bio detection, catalysis and drug delivery carriers. Given the tremendous potential of AuNPs in current biomedical topics, this review aims a thorough understanding of various methodologies on the synthesis and the recent application on the AuNPs.

II. GOLD NANOPARTICLE

Gold is a naturally occurring element and one of the components of the earth's crust. Basically, gold scientific named is Aurum with symbol Au and have an atomic number of 79. Furthermore, gold is a transition metal and located in group 11 and period 6 element. Physically, gold exists in a bright, slightly reddish yellow in its pure form and can be seen in a form of a nugget or rock-like form.

Chemically, gold is one of the least reactive elements in the form of solid state under standard conditions. Since gold is a least reactive element, it has high resistance to most acids although it does dissolve in aqua regia which is a mixture of hydrochloric acid and nitric acid. In industry, gold is very useful due to its properties which is not easily rust, tarnish resistance and least reactive thus in can be used in electrical conductors.

AuNPs is very useful even during ancient times, backdate to ancient Roman era, AuNPs were used to dye glasses to give the intense cover of different colours. Then in Egyptians era, more than 5000 years ago, they used AuNPs for mental, body and spiritual purification. While others civilization used AuNPs in medical for medicine preparation as used during the Indus era, where Saraswatharishtam and Makaradwajam had gold in it for medicinal applications. Next, Medieval artisans around 400 AD to 1300 AD have produced gold colloids with a high concentration of ruby colour by mixing a molten glass with a mixture of gold salt, and they also vary the concentration ratio to produce different coloration of glass, pottery, chinaware and ceramics [12]. The British Museum in London housed a Lycurgus Cup, which is the most perfect example of this. The Lycurgus Cup has amazing features of colour changing when light torches it. For example, if light is transmitted, it appears red, and it appears green if light is reflected.

The colour changing occurs due to exposure of light when the presence of mixed gold and argentum particle is about 70 nm diameter [13]. During the 17th and 18th century, the AuNPs were mostly used in medical field for curing various diseases, for example, it was used for detection of syphilis. Later on, in 1857, Michael Faraday founded that the formation of AuNPs by using phosphorus in CS2 to reduced chloroauric acid (AuCl4) and he also reported about the electrical properties and the special optical properties [12]. From that point onward, many methods for the synthesis of AuNPs were reported.

III. SYNTHESIS OF GOLD NANOPARTICLE

A. *Chemical Synthesis*

Generally, AuNPs are synthesised by reduction of Chloroauric acid (HAuCl4) with reduced chemical, moreover, advance and better way do exist [14]. After dissolving HAuCl4, the solution is quickly stirred with an addition of temperature while a reducing agent is added. Then Au3+ ions from HAuCl4 will be reduced to neutral gold atoms. As the number of gold atom form increased, the solution becomes saturated and the colour difference can be seen [4]. To avoid the particles from aggregating, some stabilizing agent that binds the nanoparticle surface is added and it can be functionalized with various organic ligands which can determine its functionality [2].

Various techniques of synthesis AuNPs have been developed. In 1994, Brust and Schiffrin have discovered a method to produce AuNPs in organic liquid that not are miscible with water which thermally stable and the size of diameter ranging between 2 to 6nm, later called the Burst-Schiffrin method. This method involves sodium borohydride as a reducing agent and tetraoctylammonium bromide (TOAB) solution in toluene as an anti-coagulant, phase transfer catalyst and the stabilizing agent. The Au3+ will be transferred from the aqueous phase to organic phase with the presence of thiolate to protect the AuNPs [15].

The technique by Turkevich et al. [2] has been improved by Frens [16] with a more simple method. It involves the reaction of small amounts of hot HAuCl4 with small amounts of sodium citrate solution. In this technique, sodium citrate plays a dual role: first as the reducing agent and, subsequently, the stabilizer as it is absorbed onto the surface of AuNPs [2]. The reduction of sodium citrate will reduce the amount of the citrate ions available for stabilizing the particles, and this will cause the small particles to aggregate into bigger ones (until the total surface area of all particles becomes small enough to be covered by the existing citrate ions) [7]. There is a usage of methanol electro-oxidation to produce zero dimensional hollow nanoporous AuNPs at room temperature with ligament thickness (21-54 nm) and tunable particle size (150-1,000 nm) [17]. This AuNPs include excellent specific electroactive surface area, faster mass diffusivity and large density of highly active surface sites.

B. *Bionsynthesis*

Biosynthesis of the AuNPs is the alternative way of synthesizing AuNPs without using toxic chemical. This development is very safe for either human or environment which use non-toxic methods such as the use of biodegradable reagents, synthesis in room environment, low toxicity of product and limited waste product. The method also uses components like protein, fat, carbohydrate or nucleic acid that naturally forms in the plant, flower, microorganisms such as bacteria and yeast, is an interesting research area to synthesis AuNPs in an eco- friendly and clean method [8]. The plant used for synthesis AuNPs has been a very great interest for researchers since the plant is easy to get and it also possessed a functional group that has the ability to reduce and stabilize the AuNPs and the only drawback is, it is time-consuming and have many steps for sample preparation. Table I summarizes the biosynthesis methodologies.

TABLE I
BIO-BASED AUNPS SYNTHESIS

Biological Source	**Nanoparticle Morphology**	**Size (Nm)**	**Ref**
Cucurbita Pepo L.Leaves	Sphere	10-15	[18]
Walnut (Juglans Regia) Green Husk	Sphere	14-19	[19]
Mussaenda Glabrata Leaf	Sphere And Triangular	10.59	[20]
Sphaeranthus Indicus Leaf	Sphere	25	[21]
Indigofera Tinctoria Leaf	Sphere, Triangular And Hexagonal	6-29	[22]
Sumac Aqueous Extract	Sphere	20	[23]
Elettaria Cardamomum Seeds	Sphere	15.2	[24]
Moringa Oleifera Petals	Sphere, Triangular And Hexagonal	3-5	[25]
Morinda Citrifolia L Root	Sphere And Triangular	12.17-38.26	[26]
Pogestemon Benghalensis (B) O. Ktz. Leaf	Sphere And Triangular	10-50	[27]

Biological Source	Nanoparticle Morphology	Size (Nm)	Ref
Citrus Maxima Fruit	Sphere And Rod	25	[28]
Nerium Oleander Flower	Sphere	20-40	[29]
Carica Papaya	Sphere	2-20	[30]
Catharanthus Roseus	Sphere And Triangular	3.5-9	[30]
Carica Papaya And Catharanthus Roseus	Sphere, Triangular And Hexagonal	6-18	[30]
Siberian Ginseng	Cubic	189	[31]
Stevia Rebadiauna Leaf	Sphere	5-20	[32]
Brown Macroalgae Cystoseira	Sphere	8	[33]
Penicillium Aculeatum	Sphere	60	[34]

A research has been conducted on the use of Cucurbita pepo L. leaves as the precursor for reduction of gold to AuNPs [18]. In this research the colour changes from pale green to light orange or red/purple initially when the AUNPs is formed. Characterization using TEM microscopy shows that a higher concentration of gold promotes a more monodisperse AuNPs with size range 10-15nm. They also found that the plant growth is affecting the morphology and yield of AuNPs production. The results show that the sample aged one month yield nearly spherical AuNPs. Furthermore, this method does not need high temperature to operate only at 70°C.

Izadiyan et.al [19] investigated on the use of Juglans regia (J. regia) green husk extract as the stabilizing and reducing agent for formation of AuNPs. It is reported that the synthesis of AuNPs has succeeded in which it yielded AuNPs at room and moderate temperatures at 19.19±4.7 and 14.32±3.24nm in a spherical shape. Moreover, they concluded that the increasing temperature will yield smaller AuNPs diameter size, and will increase the concentration and yield of the reaction.

The synthesis of AuNPs by using brown macroalgae Cystoseira Baccata (CB) extracts resulting a fast, eco-friendly and one-pot synthetic route and [33]. The C. baccata aqueous extract (CB) were extracted from the fresh and frozen seaweed in order to see the effect that would be given by the state of the seaweed but notably there is no different between it. This method of synthesis yielded a spherical, stable, polycrystalline nanoparticles with a mean diameter of 8.4 ± 2.2nm. CB extract acted as a protective agent which keeps the particle stay separated and prevent aggregation. Lastly, the formation of AuNPs using mycelia-free culture filtrate of Penicillium aculeatum against hydatid cyst protoscolices of E. granulosus to discover the scolicidal activity [34]. It is noted that this method yields uniform sphere shape and superior monodispersity with the average diameter of 60nm, which affirmed by SEM, AFM. UV-Vis and dynamic light scattering (DLS) analysis.

IV. APPLICATION OF GOLD NANOPARTICLE

Basically, by altering the diameter size of AuNPs and conjugated with many functionalizing agents will result in changes of its properties which also leads to its functionality. Such changes in dimension can be seen even by changing the reducing agent and manipulate other variable. Recent year shows that gold AuNPs have many applications either for detection of metal or in biomedical applications.

A. Biomedical and Drug Delivery

In recent year, there is much interest on AuNPs utilize in biomedicine, since it is small and possessed unique properties. Functionalization of AuNPs for targeted drug delivery is better compared to other drugs since it only gives an effect toward targeted area, thus increase selectivity and also lowered the side effects that may cause by conventional drug [35]. It is already shown that AuNPs that formed a linkage with protein such as antibodies still able to enter the cell [36]. Formation of drug-AuNPs complexes can increase blood half-life, protect the drug from enzymatic degradation and also enhanced drug efficacy [37].

One of the application of AuNPs in photodynamic therapy is to kill the cancer cell by heating it up. The AuNPs will be excited by light at a wavelength from 700 to 800 nm, thus enable to kill targeted cancer cell [38]-[39]. In sensor field, the used of AuNPs have widely been studied by researcher such as for detection of thiol group, human chorionic gonadotropin, cancer cell and also toxic metal [5]-[6][11], [39]-[41]. Lastly, AuNPs play huge role in delivering drug to target cell. The functionalized AuNPs with Polyethylene glycol (PEG) and 3-mercaptopropionic acid shown its ability to deliver the drug without giving cytotoxicity effect to the nucleus of Hela cells [1].

Methotrexate (MTX) was used to inhibit the proliferation of breast cancer cells MCF-7. A study has been carried out to increase the efficacy of MTX by loading the MTX to Bovine serum albumin capped AuNPs (Au-BSA-MTX) in which BSA acts as the reducing agent [42]. It shows that the Au-BSA-MTX have higher cytotoxicity toward MCF-7 cell compared to MTX alone and enhanced the proliferation activity of MCF-7 cell due to the presence of BSA as the source of nutrient and energy. A study investigated on delivery of paclitaxel (PTX) in chemo-photothermal therapy, where the Pluronic-b-poly(L-lysine) (Pluronic-PLL) as the reducing agent for the synthesis of AuNPs, which formed AuNPs coated Pluronic-PLL, which later act as drug carrier for PTX for the synthesis of AuNPs which formed AuNPs coated Pluronic-PLL [43]. This method of synthesis is considered as a green approach because no additional reducing agent and stabilizing are needed since Pluronic-PLL act as both. It is reported that AuNPs coated Pluronic-PLL show higher cytotoxicity in MDA-MB-231 cells, which is the cancer cell compared to Taxol and all results showed that it increased the cellular uptake efficiency of the drug. Thus, the in vitro and in vivo studies ensured that the combination of chemotherapy and photothermal therapy can cause more damage to the cancer cell and AuNPs coated Pluronic-PLL show potential for clinical treatment of breast cancer.

A research on the conjugation of AuNPS with gallic acid (AuNPs-GA) has been carried out to treat cervical cancer (CxCa) which is the most common cancer in women [44]. It is reported that AuNPs-GA complex is non-toxic to normal cell while GA is cytotoxic and AuNPs increased the efficacy of the GA, thus make AuNPs a better option as the photochemical deliver agent since it can inhibit CxCa cell proliferation and totally safe for normal cell. Furthermore, there is also a study on dithiolated diethylenetriamine pentaacetic acid (DTDTPA) as the stabilizing agent and $NaBH_4$ as the reducing agent to formed DTDTPA conjugated AuNPs (Au-DTDTPA) for Computed tomography (CT) enhancement and radiosensitisation in prostate cancer [45]. It is reported that 5.37 mean core Au-DTDTPA size gave a significant additional reduction in survival and delay the growth of tumor up to 38.3 days. Moreover, it also increases the CT-contrast to 10%, which clearly show that Au-DTDTPA have great potential for CT enhancement and radiosensitisation in prostate cancer.

B. Heavy Metal Detection

Heavy metal shows a great ability to form complexes, especially with biological matter, which might result in toxicological effect towards human bodies. Heavy metals are not biodegradable, and therefore they remain in ecological systems, thus the appropriate concentration of heavy metal had been restricted to be consumed in daily intake. The conventional method for detection of heavy metal in the environment used the ICP-MS, AAS, and ICP-AES. However, these instruments have shown many drawbacks such as expensive instrument and high care needed. Thus, the development of AuNPs as a sensor for metal detection is produced due to its high surface ratio volume and its optical properties to detect the heavy metal [6].

The conjugation of AuNPs with graphene quantum dots (GQDs) was used for highly sensitive and selective electrochemical sensor for heavy metal ions (Hg2+ and Cu2+) due to the unique physicochemical properties of GQDs [46]. Anodic stripping voltammetry (ASV) of GQD-AuNP modified glassy carbon electrode (GCE) in the presence of Hg or Cu ion were done by immersing preconcentrated electrode with targeted analyte. As a result, very low detection limit of 0.02 nM and 0.05 nM and high sensitivity of 2.47 µA/nM and 3.69 µA/nM for Hg2+ and Cu2+ respectively had been achieved. Furthermore, a non-field colorimetric sensing for Hg2+ in water source were studied by using thymine-Hg2+ -thymine (T-Hg2+-T) coordination chemistry, label-free detection oligonucleotide sequences were bind to AuNPs [47]. This strategy sensing mechanism is to minimize the requirement for data analysis and eliminate the use of instruments. The result of colour change was transferred on cellulose-based paper analytical devices and the data were transmitted and stored using cloud computing. The detection limit of 50 nM for the Hg2+ spiked pond and river water was reported.

A simple colorimetric method for detection of cadmium (Cd2+) AuNPs with the presence of glutathione (GSH) and NaCl had been developed [48]. Since AuNPs are easily to aggregate in concentrated NaCl solution, but the presence on GSH can prevent the aggregation process. This method was used to detect the amount of Cd2+ of rice due to rice contamination with Cd2+ in several provinces of China in 2013. The test showed the lowest detection limit with the naked eyes is 10 µM thus make this method applicable since it doesn’t need modification of AuNPs, simple and show good selectivity. Later, a better detection of Cd2+ was achieved by modification of AuNPs with DL-mercaptosuccinic acid, which formed (MSA-AuNPs) [49]. The AuNPs were synthesised by reduction of citrate ion and later addition of an aqueous solution of DL-mercaptosuccinic acid AuNPs under stirring at 3.5 h continuously. It was reported that the sensitivity of the detection is high where the linear relationships ($r > 0.9606$) in the range of 0.07 mM and 0.20 mM for Cd2+ ion were obtained. This simple, cost-effective and rapid colorimetric method for Cd2+ detection show better selectivity over metal ion, and also as a result, the detection limit is 0.07 mM by the naked eyes.

The formation of AuNPs which stabilized by cationic 1-(3-(acetylthio)propyl)pyrazin-1-iumligand denoted as APP and formed in polydispersed in size between 5 to 10 nm has been studied [50]. APP-AuNPs is used for detection of Pd2+ which showed colour changes and response to APP-AuNPs based on aggregation induced decrease of surface plasmon resonance (SPR) band. As a result, the sensor presented a sensitive and selective towards detection of Pd2+ with low detection limit 4.23 M in various concentration and pH even with the presence of other metals. Moreover, this sensor was successfully applied for Pd2 detection in tap water and human blood plasma samples. The synthesis method of this sensor is economical and simple, also rapid detection and low detection limit promise this sensor can serve as an effective tool for the Pd2+.

V. CONCLUSION

In this review, it can be concluded that the AuNPs have many potential since they have unique electrical and physical properties. AuNPs also could be prepared and conjugated with many functionalizing agents and also could be prepared by using chemical or green synthesis. Hence, AuNPs can be used as drug carries since they are no toxic and also can be used for various detection such as cancer and heavy metal.

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