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Green biosynthesis of gold nanoparticles and biomedical applications

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Abstract: Nanotechnology is an emerging field of science and technology with numerous applications in biomedical fields and manufacturing new materials. To extract gold nanoparticles with different techniques, green biosynthesis is in under exploration due to its cost effective ecofriendly preparation with controllable shape, size and disparity, tremendous physical and chemical inertness, optical properties related with surface plasmon resonance, surface modification, surface bio-conjugation with molecular probes, excellent biocompatibility and less toxicity. This review article presents the overview of green biosynthesis of gold nanoparticles (AuNP) and their recent biomedical applications.

Keywords: Biosynthesis, Gold Nanoparticles (AuNP), Biomedical Applications

1. Introduction

Nanomaterials are defined as zero or one dimensional materials with approximate size 1-100 nm. Nanoparticles are objected with three dimensions at nanoscale level. Engineered nanoparticles can be formed with different shape, size and surface chemistry, which influence optical, electronic, thermal and mechanical properties of the materials for their wide range of applications in nanotechnology. Mostly, high surface to volume ratio of nanoparticles is the key factor to enhance unique material properties. Among the variety of nanoparticles with their applications, metalic nanoparticles (like gold and silver nanoparticles) are playing most prominent role in biology and medicine [1-3]. Gold nanoparticles are enormously used for different applications such as optoelectronic devices, ultrasensitive chemical, biological sensors, catalysts, separation science, biomedical applications like drug delivery, cancer treatment, DNA, RNA analysis, gene therapy, antibacterial agent etc. [4-10]. Fig. 1 shows different recent important applications of green biosynthesized gold nanoparticles (AuNP). The synthesis of colloidal gold nanoparticles has been extensively studied for long time [11]. In 1951, Turkevich et al. suggested the synthesis of gold nanoparticles (AuNP) by reduction of Au^{3+} ions to Au^0 with the use of citric acid. This method can also be stabilized to form monodispersed nanoparticles and it could be exchanged to other ligand [12].

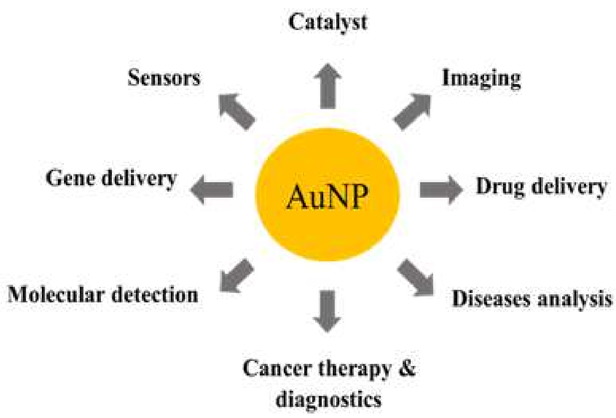

Fig. 1. *Different important applications of green biosynthsized gold nanoparticles (AuNP).*

In 1994, Brust et al. suggested the production of gold nano-particles, where sodium borhydride was used as reducing agent and citric acid was immediately replaced by selected mercaptan. This method produced monodispersed nanoparticles which was easy to disperse in organic solvent and to reisolate as pure powders [13]. Using this method, different gold nanoparticles with their modified properties such as reactivity and solubility, through changing molecular structure of thiolates on the particle surface can be produced [14-17]. However, production of gold nanoparticles with these techniques is not ecofriendly due to toxic mercaptans and organic solvents, which greatly limit to its application in biomedical field especially for clinical purpose. Thus, "green chemistry" ensures clean, non-toxic and environment-friendly methods to produce nanoparticles with well-defined shape, and controllable size [18]. The green biosynthesis of nanoparticles have more advantages over chemical or physical methods such as it has significant application in biomedical fields due to its excellent chemical stability, biocompatibility, cost effectiveness, easy preparation, optical properties related with surface plasmon resonance, convenient surface bioconjugation with molecular probes and low toxicity [19-23]. To extract nanoparticles by green synthesis mechanism, three essential features are environmentally acceptable solvent system, eco-friendly reducing and capping agents. The green biosynthesis technique are synthetic route to use relatively non-toxic chemicals for the preparation of environment friendly stable functionalize nanoparticles with the use of non-toxic solvents such as water, plant extracts, biological systems etc.

2. Green Biosynthesis of Gold Nanoparticles (AuNP)

In recent years, biosynthesized metallic nanoparticles using plant extract has been received more attention due to simple and viable alternative against chemical and physical methods with their potential applications in nanomedicine.

To prepare gold nanoparticles (AuNP), initially plant leafs are collected and completely dried with expose of sunlight. After that aqueous plant leaf extract need to prepare by mixing of 100 mL deionized (DI) water with 10 g dried leaf powder in a flask and boiled for 10-20 minutes. Then leaf extract need to add into metallic salt solution (1 mM chloroauric acid ($HAuCl_4$) solution) with 60 ^{0}C to 80 ^{0}C temperature and finally the color will change after 15-20 minutes which indicates the formation of gold nanoparticles (AuNP) [24-27]. This bioreduction of metal salt to metal nanoparticles are highly stable without impurities. Gardea-Torresdey et al. reported firstly the formation of biosynthesized gold nanoparticles using living plants [28]. They have used Alfalfa plants, which were grown in an $AuCl_4$ rich environment and found the nucleation and growth of gold nanoparticles (AuNP) inside the plant extract. The nanoparticles are in crystalline in nature with minimum 4 nm size, while large coalesced nanoparticles ranging from 20-40 nm. Dwivedi et al. reported biosynthesis of gold nanoparticles using Chenopodium album leaf extract. They have used aqueous leaf extract as mild reducing agent for nanoparticles synthesis. The biosynthesized gold nanoparticles were in quasi-spherical shapes within 10-30 nm range [29]. Fig. 2 shows the photograph of Chenopodium album leaf, transmission electron microscopic (TEM) image of leaf extract synthesized gold nanoparticles (AuNP) and their particle size distribution. The stability of the nanoparticles was determined at different pH with zeta potentiometer without adding any stabilizing agents [29].

Shiv Shankar et al. have synthesized stable gold nanoparticles (AuNP) from geranium leaves (Pelargonium graveolens) with variable size including rod, flat sheet and triangle. The shapes of particles are predominantly decahedral and icosahedral with 20-40 nm in sizes and their transmission electron microscopy (TEM) results suggest that they are multiply twinned particles (MTPs) [30]. Afterward, they synthesized thin, flat, single-crystalline gold nanotriangles (AuNP) from lemongrass plant extract, when it reacted with aqueous chloroaurate ions and then the process involve rapid reduction assembly and room-temperature sintering, resulting the formation of spherical shape "liquid like" gold nanoparticles (AuNP) [31]. The authors also extract gold nanotriangles by using lemongrass plant and found their potential application in infrared-absorbing optical coating. Fig. 3 shows transmission electron microscopic (TEM) image of gold nanoparticles (AuNP) with different shapes and sizes synthesized using lemongrass extract [32].

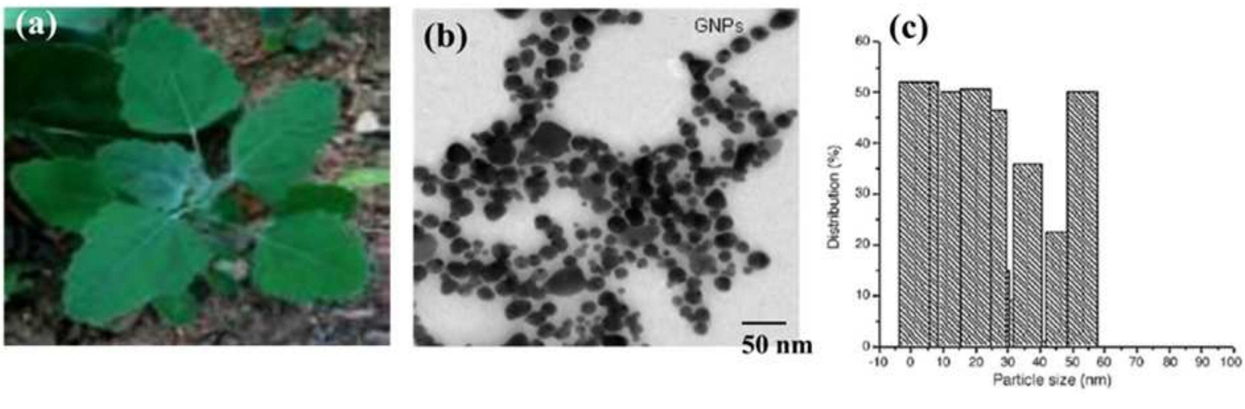

Fig. 2. (a) Photograph of Chenopodium album leaf, (b) transmission electron microscopy image of gold nanoparticles (AuNP or GNPs) and (c) histograms of particles size distribution. Permission to reprint obtained from Elsevier [29].

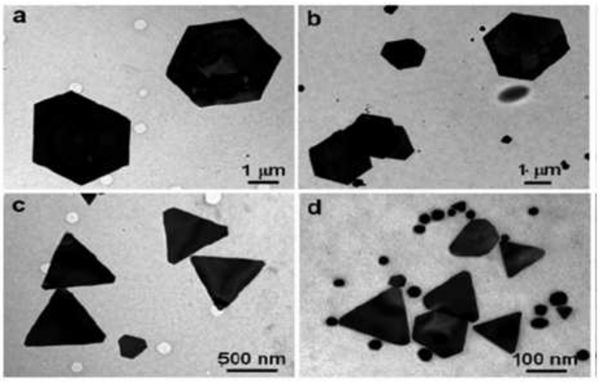

Fig. 3. Transmission electron microscopy (TEM) image of gold nanoparticles (AuNP) by the reduction of 5 mL of 10-3 M aqueous $HAuCl_4$ solution with (a) 0.2, (b) 0.3, (c) 0.5 and (d) 1.0 mL of lemongrass extract. Permission to reprint obtained from American Chemical Society (ACS) [32].

Armendariz et al. have shown gold nanoparticles (AuNP) formation with controllable size by Avena sativa biomass. They found Au(III) ions were bound to oat biomass in a pH-dependent manner and observed gold nanoparticles with fcc tetrahedral, decahedral, hexagonal, icosahedral multitwinned, irregular and rodlike shapes. The particles size influence by pH reaction, where larger particles (approximately 25-85 nm) are formed at pH 2 and smaller particles (approximately 20 nm) are observed at pH 3 and 4 [33]. Ghule et al. have reported microscale size triangular gold prisms are synthesized using bengal gram beans (Cicerarietinum L.) extract [34]. The extracellular transport of biomolecules and proteins from protein rich gram beans mediate the reduction of aqueous Au^{3+} ions and direct growth of triangular prisms. By varying the composition of gram bean extract and aqueous Au^{3+} solution, they control the morphology of gold nanoparticles [34].

Gold nanoparticles (AuNP) from sundried Cinnamomumcamphora leaf are extracted by Huang et al. using bioreduction process. The chloroauric acid ($HAuCl_4$) and dried powder of Cinnamomumcamphora leaf was used to synthesis the nanoparticles. Initially the leaf powder was added into 50 ml aqueous $HAuCl_4$ solution in the content of 100 ml conical flask at room temperature. Then the flask rotates with 150 rpm at 30 ^{0}C in a dark place resulting biomass reaction with solution and finally precipitate at the bottom of the flask within 1 hour. The suspended solution above the precipitate was collected for TEM observation. Using this technique, spherical gold nanoparticles (AuNP) were produced with different shapes ranging from 20-100 nm [27]. Again, Badrinarayanan et al. extracted gold nanoparticles (AuNP) by using Coriander leaf extract as reducing agent [35]. Here, the reduction of gold ions by Coriander leaf extract results the formation of stable morphological gold nanoparticles (size range 6.75-57.91 nm) with spherical, triangular, truncated triangular and decahedral shapes etc. The rate of reaction is rapid (12 h only) to synthesis nanoparticles by this method, when compared to microbes-mediated synthesis (24–120 h) [36, 37]. Armendariz et al. have extracted gold nanoparticles (AuNP) by the interaction of Au(III) ions with oat and wheat biomasses using cetyltrimethylammonium bromide (CTAB) or sodium citrate at pH 4. The extraction was occurred under mild condition of pH with only sonication of the samples. The sizes of the extracted gold nanoparticles using CTAB were less than 20 nm in diameter [38]. Inbakandan et al. have shown the synthesis of gold nanoparticles (AuNP) from gold precursor using the extract derived from the marine sponge, Acanthellaelongata (Dendy, 1905) belonging to the primitive phylum porifera. To produce gold nanoparticles, the marine sponge extract were added to 10.3 M $HAuCl_4$ aqueous solution at 45 °C with continuous string for 4 hours. The particles were monodispersed and spherical in shapes with size range 7-20 nm. However, the average diameters of maximum particles were 15 nm [39]. Elavazhagan et al. have synthesized silver and gold nanoparticles by the use of an aqueous leaf extract of Memecylonedule (Melastomataceae). Their scanning electron microscopy (SEM) image analysis shows that aqueous gold ions when exposed to M. edule leaf broth, gold nanoparticles (AuNP) are formed with size range 20-50 nm. However, for TEM analysis shows that formation of gold nanoparticles with triangular, circular, and hexagonal shapes with size range 10-45 nm [40]. Arunachalam et al. investigated the effect of phytochemicals present in Memecylonumbellatum leaf extract during formation of stable silver and gold nanoparticles, and found the existence of saponins, phenolic compounds, phytosterols, quinines etc. They shows that most of the phytochemicals present in the plant extract and play an important role to form silver and gold nanoparticles. In their investigation, the sizes of silver and gold nanoparticles were 15-20 nm and 15-25 nm, respectively [41]. Yasmin et al. shows the fast synthesis of gold nanoparticles (AuNP) by using a medicinal plant (Hibiscus rosa-sinensis) extract and microwave heating. To form gold nanoparticles, different conditions were optimized by varying of plant extract concentration, gold salt solution concentration, microwave heating time and power of microwave hating. The average diameter of stable spherical nanoparticles was 16-30 nm [42].

Except plant extract, gold nanoparticles (AuNP) can be synthesized using different bacteria such as Pseudomonas stulzeri, Escherichia coli, Vibrio cholera, Pseudomonas aeruginosa, Salmonell styplus, Staphylococcus currens etc. [43-49]. The bacterial synthesis of gold nanoparticles is also ecofriendly and costs effective due to its environmental compatibility, lower energy consumption etc., when compared with other physical and chemical synthesis processes. The fungi are also extremely good candidate for synthesis of gold nanoparticles (AuNP). Different reported fungi used for this purpose are Aspergillusfumigatus, Fusariumoxysporum, Penicilliumbrevicompactum, Fusariumsemitectum, Penicilliumfellutanum, Cladosporiumcladosporioides, Volvariellavolvacea etc. [50].

3. Applications

Biosynthesized gold nanoparticles have tremendous applications in different fields such as biological and chemical sensors, heavy metal ion detection, catalysts, separation science, electrical coatings etc. [51-56]. The synthesis of gold nanoparticles (AuNP) using plant extract, is advantageous over biological process by eliminating the elaborate process to maintain cell culture and also suitable for large scale nanoparticle synthesis [57]. Due to high biocompatibility, chemical stability, convenient surface bioconjugation with molecular probes, excellent surface plasmon resonance and low toxicity, biosynthesized gold nanoparticles have diverse biomedical applications including drug delivery, cancer treatment, DNA-RNA analysis, gene therapy, sensing and imaging, antibacterial agent etc. [58-60]. Gold nanoparticles have tremendous optical and electronic properties, as a result it can act as biosensors to detect biomolecules. Zheng et al. reported that, biosynthesized Au-Ag alloy nanoparticles by yeast cells can be applied for electrochemical vanillin sensor. They reported that Au–Ag alloy nanoparticles modified glassy carbon electrode was able to enhance the electrochemical response of vanillin for at least five times. In ideal condition, the peak current of vanillin can linearly increase with concentration range of 0.2–50 μM with a low detection limit of 40 nM. Using this sensor, vanillin can be detected successfully from vanillin beam and vanillin tea [61]. On the other hand, another group of scientist reported a novel nonenzymatic amperometric biosensor of hydrogen peroxide (H_2O_2) by using one-pot green synthesis to prepare a self-assembled membrane of reduced graphene oxide–gold nanoparticles (RGO–AuNP) nanohybrids at liquid–air interface [62]. The Brownian motion, electrostatic interaction between RGO and AuNP and the encapsulation of AuNP in the hybrid membrane influence the formation of RGO–AuNP hybrid membrane. The RGO–AuNP hybrid membranes are very stable in various organic and inorganic solvents. This H_2O_2 biosensor has wide linear range 0.25-22.5 mM, low detection limit 6.2 μM (S/N = 3), high selectivity and long-term stability. Hu et al. have reported green-synthesized gold nanoparticles decorated graphene sheets for label-free electrochemical impedance DNA hybridization biosensing [63]. In their work initially the graphene sheets were functionalized with 3,4,9,10-perylene tetracarboxylic acid (PTCA). PTCA molecules can separate graphene sheets and introduced more negative –COOH, which can potentially beneficial for the decoration of graphene with gold nanoparticles (AuNP). Then the amine-terminated ionic liquid (NH_2-IL) was applied for reduction of $HAuCl_4$ to gold nanoparticles. The DNA probes immobilized via electrostatic interaction and adsorption effect due to graphene sheet and NH_2-IL protected AuNP. For label free DNA detection, electrochemical impedance value increases after DNA probes immobilization. This sensor can successfully detect the sequence of pol gene of human immunodeficiency virus 1. Due to high surface to volume ratio, gold nanoparticles have very high surface plasmon resonance and can detect biomolecules. Kuppusamy et al. have detected HCG hormone in pregnant women urine sample using biosynthesized gold nanoparticles synthesized using C. nudiflora plant extract [64]. It can be used to detect HCG hormone on both pregnancy positive and negative urine sample. Initially, 500 µl of AuNP solution was mixed with same volume of the test sample and used it for assays. Then the solution was tested using a pregnancy test strip. When gold nanoparticles in the urine sample changed color into pink indicated the pregnancy, while the gray color indicated the absence of pregnancy. Authors claim this method is 100% accurate for pregnancy diagnosis and it can be used as alternative method for urine pregnancy test. Sayed et al. used biosynthesized monodispersed gold nanoparticles (AuNP) for cytotoxic assay test, biodistribution and bioconjugation with the anticancer drug doxorubicin. They produced monodispersed gold nanoparticles using thermophilic fungus Humicola spp. by green synthesis mechanism. They found Humicola spp. can reduce the precursor solution ($HAuCl_4$) at just 50 ºC to form uniform spherical morphology with high stability gold nanoparticles with size 18-24 nm. The nanoparticles are capped by natural proteins and can be directly attached with multiple-receptors such as LHRH, EGFR and EpCAM without targeting agent involvement. These nanoparticles can also bind with integrins and VEGFs for the development of novel anti-angiogenesis strategy for wide range of tumor treatment [65]. Thus the gold nanoparticles (AuNP) can use for drug delivery and cancer treatment. Malathi et al. proposed green synthesis of gold nanoparticles using chitosan as a reducing/capping agent for controlled delivery. The authors designed biocompatible carrier prepared by using single oil-in water (O/W) emulsion for controlled release of hydrophobic drugs. The drug loaded with spherical nanoparticles of size 50 nm, while the average nanoparticles size was 2-3 nm. They also investigated controlled release of rifampicin (RIF) by *in vitro* studies by using phosphate buffer saline (PBS) at pH=7.4. The encapsulated drug can release at 37 ^{0}C with 71% loading efficiency. They again investigated the antibacterial activity of RIF loaded nanoparticles by Gram +ve (Bacillus subtils) and Gram -ve (Pseudomonas aeruginosa) bacteria and drug loaded nanocarrier for treating cancer diseases [66]. Fazal et al. have shown anisotropic gold nanoparticles synthesis by using green synthesis for photothermal cancer therapy [67]. The anisotropic gold nanoparticles were synthesized using an aqueous route with cocoa extract which served as both reducing and stabilizing agent. The sizes of nanoparticles are approximately 150-200 nm, which shows good biocompatibility with A431, MDA-MB231, L929, and NIH-3T3 cell lines *in vitro* experiment with concentration of 200 μg/mL. The successful photothermal ablation was tested with epidermoid carcinoma A431 cancer cells upon irradiation with a femtosecond laser pulse of wavelength 800 nm at low power density (6 W/cm^2). This report also claims, first time green synthesized anisotropic and cytocompatible gold nanoparticles are successfully able to phototheramal therapy without using any capping agents. Krishnaraj et al. have shown *in vitro* cytotoxic effect of biosynthesized silver and gold nanoparticles against MDA-MB-231, human breast cancer cells [68]. The various silver and gold nanoparticles with concentrations ranging from 1-100 μg/ml were used for acridine orange and ethidium bromide (AO/EB) dual staining, MTT, caspase-3 and DNA fragmentation assays. The nanoparticles with concentration 100 μg/ml showed cytotoxic effects and the apoptotic with human breast cancer cells which confirmed using caspase-3 activation and DNA fragmentation assays. Hampp et al. have shown the adhesion of biosynthesized gold nanoparticles for breast cancer detection and treatment [69]. The well developed, spherical, homogeneous gold nanoparticles were synthesized using a common soil bacterium, Bacillus megaterium. The authors showed the adhesion forces between biosynthesized AuNP and breast cancer cells were almost six times greater than adhesion forces between biosynthesized AuNP and normal breast cells by using atomic force microscopy (AFM). They also reported that the adhesion force between biosynthesized AuNP and breast cancer cells were three times greater than chemically synthesized AuNP and breast cancer cells. According to their results, biosynthesized AuNP conjugated to breast-specific antibodies (AuNP-Ab conjugates) and breast cancer cells were five times greater than adhesion forces between unconjugated AuNP and breast cancer cells. These results might be useful for the development of nanostructures for targeted detection and breast cancer treatment. Craig et al. have shown functionalization of gold nanoparticles for cancer imaging. The mAb-F19-conjugated gold nanoparticles were prepared and used to label human pancreatic adenocarcinoma. Initially gold nanoparticles were coated with dithiol bearing hetero-bifunctional PEG (polyethylene glycol), and cancer-specific mAb F19. These bioconjugated nanoparticles are completely stable and used to label sections of healthy and cancerous human pancreatic tissue [70]. Mukherjee et al. have shown potential diagnostic and therapeutic applications of one-step *in situ* biosynthesized gold nanoconjugates (2-in-1 system) in cancer treatment. The gold nanobioconjugates (AuNPs-OX) were extracted using Olax Scandens leaf. From TEM observation, the gold nanoparticles were in spherical (5–15 nm), few rod shape (18–55 nm), dumbbell shape (30–55 nm), triangular (30–100 nm) and hexagonal shape (15-35 nm). The AuNP-OX nanobioconjugactes interact with different cancer cell lines such as lung (A549), breast (MCF-7) and colon (COLO205) show the significant inhibition of cancer cell proliferation in comparison with pristine Olax scandens leaf extract. The lung cancer (A549) incubated with AuNP-OX, shows significant brighter red fluorescence, when it is compared with cells incubated Olax extract leaf. Their results suggest that, the green synthesized AuNP-OX might be usefull in “2-in-1 system” for potential cancer diagnostics and therapeutic applications [71]. The production of biosynthesized gold nanoparticle and their applications has been rapidly growing interest from last decade. However, for stable nanoparticles synthesis the efficiency, controllable particles size and morphology need to improve in near future. Thus, using biological method, there is till lack of technological improvement [72-74] and we believe that, after a decade, biosynthesized gold nanoparticles (AuNP) will be widely applied in biomedical research, disease diagnosis and treatment.

4. Conclusions

In green biosynthesis mechanism, gold nanoparticles (AuNP) can be efficiently extracted by using different plants, bacteria and fungi. Due to high biocompatibily with chemical stability, surface bioconjugation, high surface plasmon resonance, higher surface to volume ratio, lower toxicity, gold nanoparticles (AuNP) can be used in various biomedical applications related to cancer diagnostics and therapeutics for the benefit of human civilization. This biocompatible nature of the gold nanoparticles is safe and efficacy for consumer health and environment. The gold nanoparticles can act as catalyst resulting to improve drug delivery efficiency, especially for the interaction between anticancer drug and DNA. However, till to date, this green biosynthesis technique is in under developed stage. This article provides some idea about biosynthesized gold nanoparticles and their applications for creating interest of the readers in this important research field. Researchers must need to give more attention to develop stable gold nanoparticles (AuNP) from different biological systems, which might be beneficial for future clinical trials.

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