OpenNano 2 (2017) 37–46

Contents lists available at ScienceDirect

OpenNano

journal homepage: www.elsevier.com/locate/onano

Recent trends and methodologies in gold nanoparticle synthesis – A prospective review on drug delivery aspect

Manimegalai Sengani[a], Alexandru Mihai Grumezescu[b], V. Devi Rajeswari[a,*]

[a] Department of Biomedical Sciences, School of Biosciences and Technology, VIT University, Vellore-14, India
[b] Politechnica University of Bucharest, Faculty of Applied Chemistry and Materials Science, Department of Science and Engineering of Oxide Materials and Nanomaterials, Bucharest, Romania

ARTICLE INFO

Keywords:
Biological synthesis
Gold nanoparticle
Photo reduction
Polymer
Laser

ABSTRACT

The prominent challenges in manufacturing carrier systems for chemical, biological and medical applications are to produce stable, nontoxic and uniform dimension particles by using various macromolecules. In this respect, the emerging field of nanotechnology enables various approaches towards optimizing synthesis protocols and methodologies. Depending on the application of the particles, various methodologies for nanoparticle synthesis have been adopted. Especially, gold nanoparticles (AuNPs) have tremendous potential for bionanotechnology-based applications, thus resulting in new possibilities and insights within the medical research field. These nanoparticles can be used for selective transportation mechanism through receptor ligand binding. During various synthesis processes of AuNps, several difficulties have been encountered. Therefore, the scientific research community turned its attention towards tuning and perfecting the obtaining approaches involved in AuNPs synthesis. This review aims to facilitate the understanding of different strategies used for AuNPs synthesis, as well as highlighting the challenges and future perspectives of AuNPs in bionanotechnology.

1. Introduction

One of the greatest challenges in anti-tumour targeted drug delivery system engineering is to develop the proper carrier tools [1]. Nano-science and nanotechnology, as emerging fields of present-day progress, enable unconventional and remarkable solutions to develop such personalized, tunable and suitable carrier platforms [2]. So far, the interest towards obtaining delivery systems that may provide controllable and targeted drug release imposingly increased, so there is an arsenal of nanotechnology-based carriers that were developed and successfully reported for such provoking applications. Especially, metallic nanosystems have gained great consideration regarding this peculiar research field thanks to their novel size-dependent properties and behavior, which strongly recommend them as stable and suitable tools for targeted, controlled and sustained drug release. Among the successfully developed and examined metallic nano-sized particles, gold nanoparticles (AuNPs) are explored for various nanotechnology-related biomedical applications, considering thus their nontoxicity and unique optical, physicochemical and biological properties [3]. Thanks to the size-dependent quantum confinement behavior of metallic nanoparticles, gold nanoparticle surface exhibits a peculiar surface plasmon resonance (SPR) phenomenon, resulting in strong extinction of radiating light wavelength. This unique activity related to AuNPs optical features – which is missing in bulk material – is conferred by the collective oscillation of free conduction electrons within the metal after interaction with the concerned electromagnetic field [4]. As shown in Fig. 1, the SPR band related to AuNPs is specifically

* Corresponding author.
E-mail address: sdevirajeswari@gmail.com (V.D. Rajeswari).

http://dx.doi.org/10.1016/j.onano.2017.07.001
Received 30 January 2017; Received in revised form 4 July 2017; Accepted 4 July 2017
Available online 06 July 2017

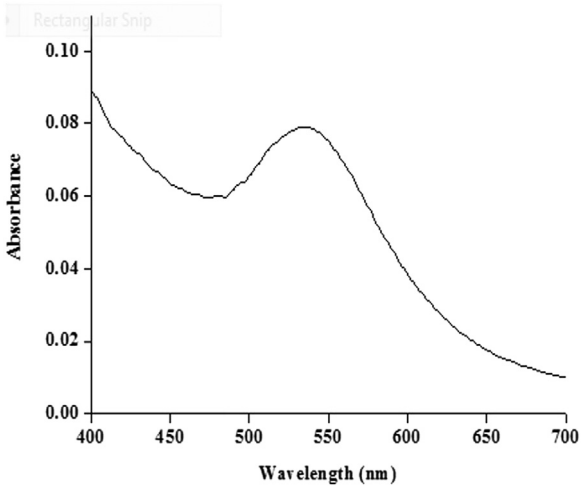

Fig. 1. UV–Visible spectra of synthesized AuNPs.

located at 530 nm, when using a scanning wavelength between 200–700 nm, corresponding to middle and near ultraviolet and visible electromagnetic radiation. This unique optical behavior related to AuNPs works thoroughly different from the bulk counterparts, thus resulting in novel nanosystems for unusual challenging optical-related applications.

The surface charge of AuNPs, estimated in terms of zeta potential, facilitates their physicochemical stability and further implementation in the cellular process and bioaccumulation. As plenty previous research studies have revealed, the toxicity level assigned to AuNPs is strongly dependent on the particle surface charge, thus the positively charged gold nanoparticles cause cell death at a lower concentration, while the neutrally charged particles determine cellular death at significantly higher concentration [5]. Collectively, one can conclude that the gold nanoparticle surface charge plays a critical role during the fabrication process of nanosystems with potential applications in controlled and targeted drug therapy. Considering these singular properties of AuNPs, but also the current challenges towards a personalized medical care, gold nanoparticles possess the attractive potential for engineering novel nanostructured tools for selective tumour targeting and imaging, emphasizing thus their tremendous potential in unconventional cancer diagnosis and treatment [6]. The current progress reported in nanotechnology enables the successful synthesis of AuNPs with an average particle size lower than 10 nm, which can experimentally be determined by Diffraction Light Scattering (DLS) means. The crystalline nature and the crystallite size of the synthesized AuNPs can be examined through X-Ray Diffraction (XRD) analysis and further confirmed by Selected Area Electron Diffraction (SAED) technique (as an additional analysis tool within the Transmission Electron Microscopy equipment). The TEM analysis offers relevant data regarding the inner surface and shape, the dimensional range and size distribution of the gold nanoparticles. The size of the AuNPs is a crucial aspect towards the development of performing nanogold-related systems since it is responsible for their bioavailability, bioaccumulation, and toxicity in a biological system. Considering the nanotechnology-related attractive strategies of manipulating matter at an atomic or molecular scale and the peculiar features and potential use of AuNPs in various up-to-date applications, there were successfully performed different approaches for gold nanoparticle synthesis [7].

AuNPs are considered as one of the most convenient carrier systems, given their enhanced biocompatibility, stability and oxidation resistance. Thus, colloidal gold is applicable in various medical-related research fields, including biosensing and bio detection, catalysis and bioelectronics, drug delivery carriers and macromolecular carriers, bioimaging and photo hyperthermia [8]. Given the tremendous potential of colloidal nanogold in current biomedical topics, this review aims a thorough understanding of various methodologies and recent trends that are involved in reduction of gold (III) derivatives into gold colloids.

2. Conventional chemical synthesis of colloidal gold

Among the conventional methods used for AuNPs synthesis, the reduction of gold (III) derivatives, namely $HAuCl_4$, by aqueous citrate solutions was successfully proposed by Turkevitch in 1951. As the authors have experimentally observed, the ratio between the reducing agent and stabilizing agent significantly influenced the size of the obtained nanoparticle [9]. Along with the usage of the metallic salt of chloroauric acid as a gold precursor, use of various concentrations of borohydride also enabled the production of nanogold with different sizes and morphologies, like nanorods and nanowires, spherical and triangular AuNPs [10]. The authors stated that the reduction of concerned metallic precursor in presence of ascorbic acid and CTAB occurs at very slow rate. By using aqueous surfactant-based colloidal chemical method in the presence of ascorbic acid and CTAB, anisotropic metallic nanoparticle can be experimentally synthesized and this method is further applied in semiconductor systems [11]. Though some chemical synthesis strategies led to the production of reduced stability and highly agglomerate AuNPs, those aspects can be overcome by using a two-phase liquid-liquid system. For example, promising data have been reported by using thiol derivatives (like toluene),tetraoctyl ammonium bromide (as phase-transfer reagent) and borohydride reducing agent in the presence of dodecanethiol ($C_{12}H_2SH$) [12]. Herein, a two phase redox reaction was carried out by using two reducing agents. Recently, a novel one-step synthetic approach

consisting in using methanol electro-oxidation at room temperature was successfully used to produce zero-dimensional hollow nanoporous AuNPs [13]. This novel zero-dimensional gold-based nanosystem comprises large density of highly active surface sites, faster mass diffusivity and excellent specific electro-active surface area. The size-dependent behavior of gold nanoparticles and their nano-related property enhancement lead to the tremendous potential of AuNPs in rat brain cancer treatment, as the experimental studies have shown [14]. At present AuNPs are used as labelling material in therapeutics and diagnostics tool for different diseases. Conjugation of peste des petits ruminants (PPR) antibody with colloidal AuNPs synthesis was very good for preparation of PPR diagnostic strips [15]. Conventionally synthesized colloidal gold functionalized with α-fetoprotein antibody useful biomarker in malignant detection [16]. Citrate mediated synthesis of polydispersed colloidal gold meet the need of large scale manufacturing for industrial and commercial purpose [17]. At the same time, a comparative study shows radiolytical degradation of citrate ion produced stronger reducing agents than citrate ions themselves [18].

3. Polymer-mediated synthesis of colloidal gold

Controlling the size and shape of nano-gold represents an important aspect in colloidal gold synthesis. As various research studies have shown, the interaction of gold metallic nanoparticles with polymers strongly impact the size, stability, and distribution of particles [19]. A common and significant aspect related to cancer treatment refers to multi drug resistance, which is a fundamental obstacle in effective chemotherapeutic therapy. Wang et al. have experimentally shown that this circumstance can be overcome by using doxorubicin entrapped into a poly (ethylene glycol) capping layer immobilized through an acid-labile spacer. According to the reported data, such a system will significantly increase the efficiency of both intracellular uptake and release of anti-tumour drug [20]. Caroline et al. suggested a simple solution phase reduction strategy to overcome the above mentioned aspects. The authors reported that metallic ions have been successfully attached to the polymer backbone of poly-(methylphenylphosphazene) (PMPP), thus preventing further crystallite growth under ambient glass transition temperature (*Tg*) and enabling additional size control by varying the concentration of PMPP [21]. In order to enhance the stability of polymer mediated synthesized gold nanoparticles performed by enriched encapsulation of dimers, Xinjiao et al. have successfully reported novel nanogold-based systems consisting of citrate reduced AuNPs encapsulated within the 154 block copolymer of polystyrene and poly (acrylic acid) via hydrophilic and hydrophobic interactions [22]. The featured article states that polymer inspired AuNPs functionalised architecture such as 1D nanowires, 2D films and 3D nanodevices [23]. Polymer brushes prepared by using AuNPs core shell having polymer nanowires [24]. Among colloidal synthesis by using polymer, DNA also considered to be one of the best polymer material, due to the specificity of DNA base-pairing, the physicochemical stability, its predictability of inter- or intramolecular interactions, and mechanical rigidity [25]. Along with that DNA can be easily modified through restriction enzymes, DNA polymerases and ligases which make more powerful and desirable nano-preparations [26].

4. UV-induced photochemical synthesis of colloidal gold

The promising potential of AuNPs in powder metallurgy, photocatalysis, magnetic device fabrication, aerosol and chemisorption applications is strongly dependent on the shape and size of the synthesized nanoparticle [27]. Controlling the morphology and dimensional features of gold nanoparticles is an attractive and challenging aspect of colloid chemistry, but the tremendous progress reported in nanotechnology enabled to involve and explore several novel strategies during the development of this process (Fig. 2).

As various research studies have reported, the photoreduction process enables the formation of single crystallite-based gold nanoparticles. The synthesis of colloidal gold with controllable size nanoparticles was successfully performed by photochemistry by Shengchun Yang et al. [28]. Macromolecular polymers, dendrimers and surfactants act as soft templates during AuNPs fabrication, by providing the required steric hindrance effect and thus preventing the aggregate formation. The presence of UV radiation with different wavelengths (transilluminator light source, 48 W) will encourage chemical reactions with aqueous Au (111) solution and the presence of surfactant/polymer reagent will specifically impact the particle dimensions, meaning that the particle size will decrease by increasing the polymerization degree [29]. Functionalized colloids with heparin were prepared assisted with UV black-

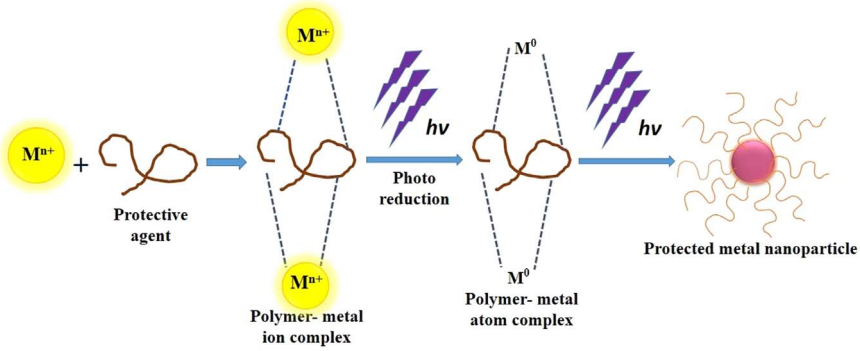

Fig. 2. UV irradiation conditions the protective action of polymer or coordination compound for the reduction process of Au (III) ions can be illustrated.

light lamp irradiation about λ = 366 nm. This negatively charged AuNPs were used for the Surface Enhanced Raman Spectroscopy (SERS) [30]. An aqueous solution of chloroauric acid with γ-rays irradiation from 80 nm colloidal gold. Gama radiation, highly energetic hydrated electrons with lifetimes of the order of microseconds ensure fast nucleation of the metal ions. But under UV radiation, ketyl radicals with millisecond lifetimes enhance the probability of reduction of metal ions over longer timescales, thereby opening the possibility to modulate particle shape [31].

5. Ultrasound-assisted synthesis of colloidal gold

Ultrasound wave generator (Kaijo 4021 type, 200 kHz frequency, 20–200 W) was used for a water bath with constant temperature for the ultrasonic-assisted reduction of gold ions in presence of 2-propanol [32]. For reproducibility and tunability reasons, various stabilizers have been used during the conventional ultrasound-assisted synthesis method, such as citrate, poly (N-vinyl-2-pyrrolidone), triphenylphosphine, disulphide and several dendrimers [33]. Using the ultrasonic field during the experimental fabrication of AuNPs is an attractive and facile strategy for colloidal gold synthesis that can be successfully used during both chemical and biological synthesis methodologies.

6. Laser ablation synthesis of colloidal gold

By using the laser ablation strategy during the synthesis process, accurate and reproducible results have been obtained, in terms of dimensional and morphological aspects. Thus, the pulsed laser deposition method – which requires concurrent evaporation-condensation phenomena of bulk gold – represents a full-fledged physical approach that can be successfully used to produce AuNPs with tunable features [34]. The synthesis mechanism requires reduction of gold (III) tetrachloroaurate metallic precursor by considering the photo-induced effects of a 532 nm wavelength laser beam, thus producing nanogold particles with size range lower than 5 nm. Within this process, aqueous solutions of sodium dodecyl sulphate (SDS) has been used as a template agent and the authors have studied the influence of both SDS concentrations and laser influences on the dimensions of the synthesized AuNPs [35]. Gold nanoparticles obtained through laser ablation applied in immunochromatographic assay labelling [36]. A two-step laser assisted ablation methodology synthesized colloids enhanced Surface Raman scattering (SERS) and bio-imaging in vivo applications. Laser activated nano-rods applicable in bridging connective tissues in the field of biomedicine [37]. Gold nanospheres, silica – gold nanoshells and gold nanorods have wide range of application in biological and cell imaging applications, as well as for photothermal therapeutic applications [38].

Given the versatility of both physical and chemical synthesis strategies used for colloidal gold fabrication, various technologies have been successfully used during the last research studies, including aerosol-based synthesis, ultraviolet and ultrasound radiation, lithography, laser ablation and photochemical reduction of metallic gold. However, these physicochemical synthesis approaches often require using hazardous chemicals expensive equipment and technologies, so the attention of research community recently turned into the bio-inspired methodologies for AuNPs synthesis.

7. Unconventional synthesis of colloidal gold

In general, the chemical synthesis of gold nanoparticles consists in low cost technologies applicable for high volumes, which provide quite reproducible results (in terms of size and shape). However, there are some specific drawbacks of the chemical synthesis, including using toxic solvents, contamination from precursor chemicals and production of hazardous derivatives [39]. In order to overcome these complications, biological-based synthesis approach became an important direction of current nanotechnology-based research. There is a wide range of biological sources that are available in nature and can be successfully revalued during the synthesis process of colloidal nanogold, including plant-based compounds and derivatives, bacteria, fungi, algae, yeast and viruses [40].

8. Microbial mediated synthesis of colloidal gold

The need of cost effective and eco -friendly synthesis of AuNPs by using microbes are emphasized because of no hazardous chemicals and toxic derivatives. The mechanism has been postulated that enzymes like ligninases, laccases, reductases and peptides are involved in growth and nucleation of NPs [41]. Free cysteine/amino and surface bound protein of microbes involved in stabilization of these colloids [42]. During synthesis there are several factors like temperature, pH, substrate concentration, and static condition influence the synthesis and stability of AuNPs [43]. However, there are plenty of studies available on optimizing these protocols. Prema et al. stated that *Klebsiella pneumonia* mediated synthesis of AuNPs and synergetic effect of antimicrobial property towards various bacterial pathogen *E. coli, S. epidermidis, S. aureus, P. aeruginosa* and *B. subtilis* [44]. The fungus *Penicillium crustosum* isolated from soil involved in success full synthesis of AuNPs mediated by extracellular proteins [45]. Another study reported bioreduction of *Actinomycetes, Thermomonospora sp* are readily synthesized AuNPs [46]. *Glucono-bacter oxydans* immobilized on the graphiteelectrode via sol – gel (tetraethyl ortho silicate)/chitosan hybrid composite gold nanoparticles useful in whole cell biosensor was designed and characterized using glucose as the substrate [47].

Both the eukaryotes and prokaryotes have the ability to synthesize gold colloids from inorganic precursors, given the specific activity of their secondary metabolites produced either intracellular or extracellular.

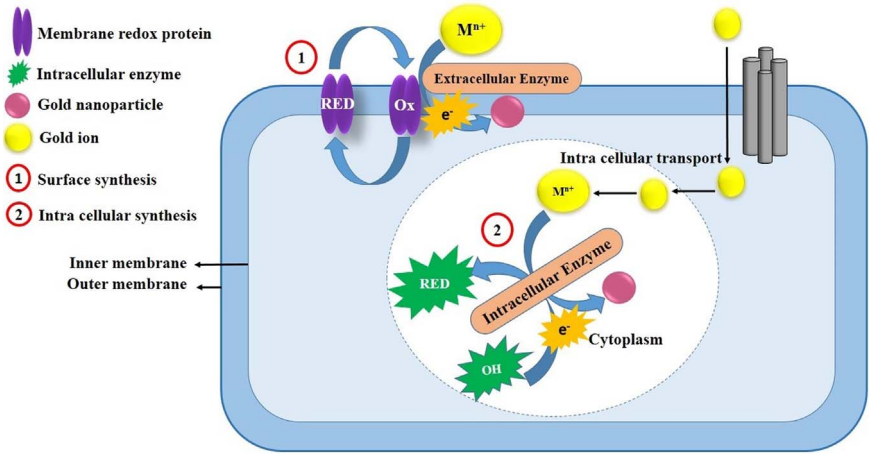

Fig. 3. Mechanism of extracellular and intracellular synthesis of AuNPs.

9. Extracellular synthesis of colloidal gold

The extracellular synthesis approach of AuNPs refers to the reduction-based mechanism of chloroauric ions in presence of cells, the biosynthesis successfully occurring due to the key role of the cell wall and cell wall proteins. A schematic representation of the bio-inspired synthesis mechanism of gold nanoparticles is depicted in Fig. 3. The performed experimental studies have revealed that the *Enterobacteriaceae* culture supernatants are enriched in nitro reductase enzyme content that is subsequently involved in bacterial mediated synthesis of colloidal gold [48].

When it comes to yeast mediated nano-gold synthesis, the oxido-reductase enzymes, and the quinones were successfully involved in the metallic gold reduction process [49]. Among the microorganism-mediated synthetic methodologies that are summarized in Table 1, the fungi mediated synthesis of colloidal gold is considered as the best bio-inspired option, given the fact that fungal strains are capable to secrete large amount of extracellular enzymes with distinctive functions. Especially, the externally secreted fungal proteins including α-NADPH-dependent sulfite reductase, various hydrolases and amylases, different cellulase and proteases have been successfully involved during the reduction process of metallic gold ions [50]. The performed studies have reported that *Fusarium oxysporum* particularly secrets two distinctive extracellular proteins with 24 kDa and 28 kDa molecular weights that are responsible for biosynthesis of zirconia nanoparticles [51]. Park et al. reported that the evolution of green chemistry approach in manufacturing inorganic nanoparticles protected by aqueous soluble secondary metabolites – such as alkaloids, terpenoids, phenolic compounds,

Table 1
Bio-inspired synthesis of gold nanoparticles.

Biological source	Nanoparticles morphology	Size [nm]	Biosynthesis location	References
Bacteria				
Bacillus subtillus	Octahedral	5-25	Intracellular	[56]
Pseudomonas aeruginosa	Spherical	5–30	Extracellular	[57]
Escherichia coli	Triangular	25–33	Intracellular	[58]
Rhodopseudomonas capsulata	Spherical	10–20	Extracellular	[59]
Stenotrophomonas maltophilia	Spherical	40	Extracellular	[60]
Brevibacterium casei	Spherical	10–50	Extracellular	[61]
Bacillus licheniformis	Cubic	10–100	Intracellular	[62]
Pseudomonas veronii	Different shapes	5–25	Extracellular	[63]
Klebsiella pneumoniae	Spherical	35–65	Extracellular	[64]
Marinobacter pelagius	Spherical	> 20	Extracellular	[65]
Geobacillus sp. *strain ID17*	quasi-hexagonal	5–50	Intracellular	[66]
Fungi				
Fusarium oxysporum	Spherical and Triangular	8–40	Intracellular	[67]
Rhizopus oryzae	Different shapes (rod, triangle, hexagon)	9–10	Intracellular	[68]
Algae				
Shewanella algae	Different shapes (triangular, hexagonal, nanoplates)	~10	Extracellular	[69]
Sargassum wightii Greville	Spherical	8–12	Extracellular	[70]
Chlorella vulgari	Different shapes (triangular, truncated triangular, hexagonal)	800–2000	Extracellular	[71]
Plant				
Aloe vera	Triangular	2–8	Extracellular	[72]
Cassia auriculata	Triangular, hexagonal	15–25	Extracellular	[73]
Hibiscus rosa-sinensis	Spherical	16–30	Extracellular	[74]
Ananas comosus	Spherical	10–11	Extracellular	[75]

and co-enzymes – is a growing, attractive and promising research direction of novel nano-based technology. As the experimental data have shown, these secondary metabolites were successfully involved in reduction-based processes of soft metal to produce nanosized particles [52].

10. Intracellular synthesis of colloidal gold

Gardea-Torresdey et al. have examined and explained for the first time the intracellular formation of gold and silver nanoparticles inside living plants [53]. The performed study included growing the Alfalfa plants in $HAuCl_4$ rich environment and the obtained data revealed that the aforementioned plant has the tremendous ability to in situ produce inorganic nanoparticles within the vegetal cells. Growing *Sesbania drummondii* seedlings in chloroaurate solution resulted in the accumulation of stable gold nanoparticles within various plant tissues, as a consequence of shoot-guided transport phenomena of the root-located reduction processes [54]. The as-obtained intracellular monodispersed and immobilized gold nanoparticles may act as stable catalysts for future applications. Also, for the *Brassica juncea* cultures grown under gold mine soil, it has been reported that the plant has the ability to chemically reduce gold ions and to decrease the amount of nanoparticles embedded within the vegetal tissue. After enzymatic digestion, the dimensional range of the as-produced AuNPs was comprised between 5 nm and 50 nm, while after biomass calcination process the final product contained 100–1000 nm sized particles [55]. The intracellular biosynthesized gold clusters capped with organic ligands have the ability to covalently attach to biological substances and structures and protein molecules, resulting thus promising nanotools with biological labelling potential applications.

11. Plant mediated synthesis of colloidal gold

Plant mediated synthesis of inorganic nanoparticles has various advantages in comparison with the microbial synthesis, including the avoidance of time consuming maintenance of cell cultures and the opportunity to produce massive amounts of nanoparticles at a large industrial scale [76]. The mechanism-guided synthesis process consists in revaluing the polyphenol-based secondary metabolites from plants as efficient reducing agent for metallic precursors. The identified hydroxyl groups within the plant-derived polyphenols were found to be successfully involved in gold ions reducing process, by encouraging the oxidation reaction and the specific formation of quinine forms [77]. The above mechanism occurs according to Pearson acid-base concept (HSAB theory), which explains that hard acids prefer to coordinate hard bases to form ionic complexes, while soft bases prefer to coordinate soft acids to form covalent complexes [78]. When a hard ligand specifically binds soft metals (like Au^+), no complex compound will be encouraged to form; instead, the concerned soft metal will undergo reduction processes and finally form AuNPs (Fig. 4).

Further, the stability of the synthesized AuNPs can be achieved by electrostatic interactions that limit their additional growth [79]. When it comes to plant mediated synthesis of gold nanoparticles, except for the required complex bio reduction processes, there are several factors that may impact the synthesis evolution, including temperature, pH and concentration of reductive biomass.

Song et al. reported that *Magnolia kobus* leaves extract can be successfully used to eco-friendly synthesize AuNPs [80]. In this experimental report, the authors revealed a reverse dependency between the size and shape of the obtained nanoparticles and the synthesis temperature. According to the obtained results, by performing the synthesis process at 25 °C led to the formation of AuNPs with 5–300 nm mean size, while the same experiment performed at 95 °C led to the synthesis of 5–7 nm sized nanogold. Also, the author reported that a thin layer of plant-derived organic material was protected the inorganic gold nanoparticles (acting as a capping agent), increasing thus the physicochemical stability of the nanogold-based systems up to 4 weeks. The biomass resulted from oats (*Avena sativa*) was also used for successful gold ions reduction, the as-obtained multi-shaped nanoparticles being synthesized by considering various pH values [81]. This study reported that large sized nanoparticles were obtained when considering strong acidic conditions (pH = 2), while AuNPs with smaller sizes were achieved when using mild acids (pH = 5, respectively pH = 6). During these biological synthesis processes, the secondary metabolites pertaining to various plant structures (including leaf, stem, root,

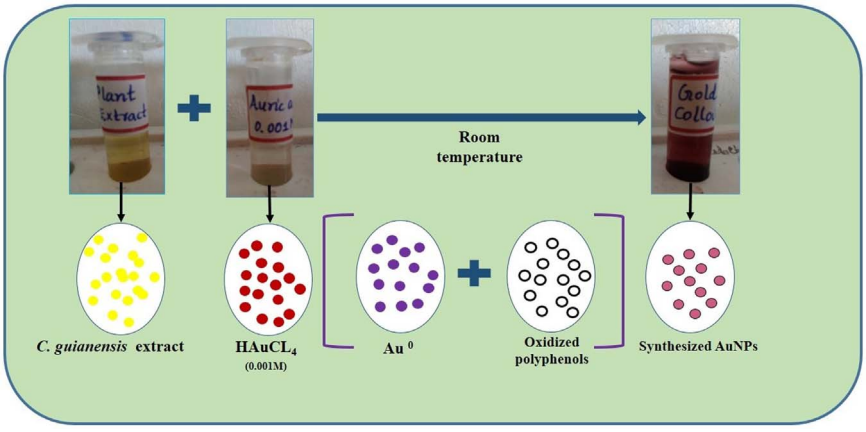

Fig. 4. Plant polyphenol mediated synthesis of AuNPs and mechanism.

vegetable, fruit, seeds and biomass) may be successfully revalued as an active component of the synthesis process.

12. Leaf mediated synthesis of colloidal gold

When considering the leaf mediated synthesis of AuNPs, it is worthy to mention that most of the experimental studies have oriented their attention towards the medicinal herbs extracts [82]. This synthesis approach requires the revaluation process of isolated compounds from medicinal herbs that are produced at a large scale for pharmaceutical applications. These herbs-derived active compounds are polyphenols that possess heavy ligands involved in reduction and stabilization of metallic gold ions. Besides, the bioavailability and therapeutic efficiency of such biosynthesized nanosystems will be higher than that of pristine gold nanoparticles, respectively than the drug alone [83]. Based on some recent research studies, various plants with medicinal potential have been successfully used for AuNPs photo-mediated synthesis, including *Jatropa curcas* L. (Barbados nut), *Tridax procumbens* L. (Coat buttons), *Solanum melongena* L. (Eggplant), *Calotropis gigantea* L. (Calotropis), *Carica papaya* L. (Papaya) and *Datura metel* L. (Datura) [84]. *Ocimum sanctum* (*Krishna tulsi*, Indian holy basil) is a well-known Indian medicinal plant which aqueous extract have been successfully used for experimental synthesis of AuNPs [85]. The active compounds isolated from *Ocimum sanctum* extract – namely apigenin, cirsimaritin, rosmarinic acid, estragole, linalool, carvacrol and urosolic acid – were reported for pharmaceutical applications and the hard ligands of these compounds were found to have the ability to reduce metallic ions. The poly-dispersed gold nanoparticles were experimentally produced by using the extracellular reduction of gold precursors in presence of high concentrations from neem leaves extract [86]. Here, the flavonoid and terpenoid molecules were involved in surface stabilization of AuNPs. The isolated therapeutic compounds reported for *Coriandrum sativum* L. extracts (5-feruloylquinic, 5-p-coumaroylquinic acid, rutin, dicaffeic acid, feruloylquinic and caffeoylquinic acid) were used for the biosynthesis of AuNPs with dimensional range from 6.75 nm up to 57.91 nm [87]. Bonde et al. elaborated a new synthesis protocol for gold nanoparticles by using the *Murraya koenigii* leaf extract to experimentally reduce gold ions and stabilize inorganic nanoparticles with 20 nm average size [88]. The phytochemical analysis further revealed that this plant contains rich sources of phenolic compounds with strong antioxidant potential.

13. Fruit mediated synthesis of colloidal gold

The effects of dietary polyphenols possess a significant role in human health. According to the latest reported data, the plant-derived polyphenols are strongly involved in preventing neurodegenerative disorders, diabetes and cancer conditions [89]. Generally, fruit and fruit pulp are considered to be rich sources of readily available polyphenols. The reaction between gold ions and citrus fruit (*Citrus reticulate, Citrus limon*, and *Citrus sinensis*) led to the extracellular synthesis of gold nanoparticles at boiling temperature [90]. Complementary investigations have explained the successful use of *Emblica officinalis* extracts during the rapid reduction of chloroauric ions, resulting thus stable, morphological and dimensional uniform particles, with an average size of 25 nm [91]. Ghodake et al. have obtained AuNPs with different shapes (spherical, hexagonal and triangular) by using the rapid biosynthesis process of metallic gold ions in presence of pear fruit extract [92]. Another study has reported the successful use of crushed, boiled, acetone-precipitated and air-dried banana peel powder to reduce chloroauric acid. At standard synthesis condition (in terms of ambient temperature and humidity), the obtained nanogold particles sized up to 300 nm. AuNPs were also prepared by using the *Prunus domestica* (plum) fruit extract, the as-synthesized particles considering the additional catalytic effect of 4-nitrophenol [93].

14. Bark mediated synthesis of colloidal gold

Daisy et al. have successfully reported the synthesis of gold nanoparticles by using the *Cassia fistula* bark extract, the resulted nanosystems presenting a tremendous potential for hyperglycemia treatment [94]. Other research study mentioned that the stem extract of *Breynia rhamnoides* enabled the reduction of gold nanoparticles by revaluating the catalytic reduction of 4-nitrophenol [95]. The bark extract from the traditional *Dalbergia sissoo Roxb* Indian plant was also successfully used for the reduction of gold ions, thanks to the rich content of antioxidants within this plant [96]. The obtained AuNPs have experimentally revealed a promising potential against many reactive oxygen species (ROS) induced disorders.

15. Seed mediated synthesis of colloidal gold

The seed portion of a plant contains more antioxidant agents than the edible portions. According to phenol explorer data base, 100 dietary sources of polyphenols were examined and the reported results emphasized that seeds provide the most consistent and useful source of polyphenols [97]. When using seed extracts to extracellular biosynthesise AuNPs, the experimental data revealed that the obtained gold nanoparticles were capped with a rich polyphenol-based layer and possess an attractive and promising potential for treating several disorders [98]. Along with the phenolic compounds, seeds are also rich sources of amines and proteins. It has been reported that AuNPs (62 nm mean size) synthesized in presence of *Abelmoschus esculentus* seed extract showed excellent antifungal activity against *Puccinia graministritci, Aspergillus flavus, Aspergillus niger* and *Candida albicans fungal strains* [99]. Except for the seed extracts, seed oils have also been used during the synthesis of gold nanoparticles. When it comes to seed oils, properties like dispersion, viscosity, polarity, vapour pressure and optical activity are crucial aspects that encourage the stabilization of the synthesized gold nanoparticles, by preventing the profuse crystal growth [100].

Among vegetable seed-based oil, the castor oil (*Ricinus communis*) is considered to have the adequate viscosity and polarity, which are physical aspects considered during the conversion process of gold ions into gold nanoparticle in presence of $NaBH_4$ reducing agent

[101].

16. Macro molecule mediated synthesis of colloidal gold

The aqueous synthesized nanoparticle functionalized with biomolecules (DNA, antibodies, proteins, and peptides) are trending techniques [102]. In general multifunctional peptide coated AuNPs having potential affinity and specificity towards biological and inorganic surfaces which exhibit bio molecular recognition [103]. Recently peptide macromolecule as used as source for the reduction of metal ions to nanoparticles in the presence of $NaBH_4$. The peptide coated AuNPs are exist as spherical in shape and exhibit catalytic activity for the reduction of 4-nitrophenol [104]. Christof et al. reported that convenient colloidal gold functionalised with DNA/ proteins. These bimetallic hybrid components are selectively suited for the analysis of protein microarrays, which are increasingly applied in bio-analytical field like proteomic research and immunological diagnostics [105]. Juewen Liu and Yi Lu stated DNA and RNA bound with gold nanoparticle to prepared sensitive probe in colorimetric sensor [106].

17. Conclusion

In this review, we provide the reader an overview regarding both conventional and unconventional synthesis strategies for gold nanoparticles. Among the available synthesis methodologies, the biological-based synthesis approach is considered to be the best option, considering thus its invincible advantages (in terms of ease and eco-friendly aspects, tunability and reproducibility). The tremendous potential of nanotechnology-guided AuNPs-based systems represents an attractive research field for current science community, including the biomedical research. Given the physicochemical features of AuNPs and their versatility (in terms of morphological and dimensional aspects, but also physical, chemical, biological and immunological behaviors), gold nanoparticles possess a remarkable potential for various biomedical-related applications, including targeted and controlled drug delivery platforms, biodetection and biomedical imaging platforms, (photo)hyperthermia and gene therapy. For either of the above mentioned research directions, it is crucial to develop sized and shaped uniform AuNPs, but also stable and non-harmful AuNPs with adjustable features, providing thus making them the ideal candidates for the nanotechnology-based development of personalized healthcare practice.

Acknowledgement

I would like to acknowledge VIT University, Vellore-14, for their better infrastructure to carry out our work.

References

[1] G.L. Semenza, Targeting HIF-1 for cancer therapy, Nat. Rev. Cancer 10 (2003) 721–732.
[2] G.M. Whitesides, Nanoscience, nanotechnology, and chemistry, Small 2 (2005) 172–179.
[3] R.M. Tripathi, A. Shrivastav, B.R. Shrivastav, Biogenic gold nanoparticles: As a potential candidate for brain tumor directed drug delivery, Artif. Cell Nanomed. B. (2014) 1–7.
[4] P. Pattnaik, Surface plasmon resonance, Appl. Biochem. Biotechnol. 126 (2005) 79–92.
[5] H. Chunbai, Y. Hu, L. Yin, C. Tang, C. Yin, Effects of particle size and surface charge on cellular uptake and bio distribution of polymeric nanoparticles, Biol. Mater. 13 (2010) 3657–3666.
[6] J. Jiang, G. Oberdörster, P. Biswas, Characterization of size, surface charge, and agglomeration state of nanoparticle dispersions for toxicological studies, J. Nanopart. Res. 11 (2009) 77–89.
[7] T.K. Sau, C.J. Murphy, Room temperature, high-yield synthesis of multiple shapes of gold nanoparticles in aqueous solution, J. Am. Chem. Soc. 126 (2004) 8648–8649.
[8] L. Dykman, N. Khlebtsov, Gold in biomedical applications: recent advances and perspectives, Chem. Soc. Rev. 41 (2012) 2256–2282.
[9] J. Polte, T.T. Ahner TT, F. Delissen, S. Sokolov, F. Emmerling, A.F. Thünemann, R. Kraehnert, Mechanism of gold nanoparticle formation in the classical citrate synthesis method derived from coupled in situ XANES and SAXS evaluation, J. Am. Chem. Soc. 132 (2010) 1296–1301.
[10] M. Grzelczak, J. Pérez-Juste, P. Mulvaney, L.M. Liz-Marzán, Shape control in gold nanoparticle synthesis, Chem. Soc. Rev. 37 (2008) 1783–1791.
[11] T.K. Sau, C.J. Murphy, Room temperature, high-yield synthesis of multiple shapes of gold nanoparticles in aqueous solution, J. Am. Chem. Soc. 126 (2004) 8648–8649.
[12] M. Brust, M. Walker, D. Bethell, D.J. Schiffrin, R. Whyman, Synthesis of thiol-derivatised gold nanoparticles in a two-phase liquid–liquid system, J. Chem. Soc., Chem. Commun. 7 (1994) 801–802.
[13] S. Pedireddy, H.K. Lee, W.W. Tjiu, I.Y. Phang, H.R. Tan, S.Q. Chua, C. Troadec, X.Y. Ling, One-step synthesis of zero-dimensional hollow nanoporous gold nanoparticles with enhanced methanol electrooxidation performance, Nat. Commun. 17 (2014) 5.
[14] R. Kopelman, Y.E. Koo, M. Philbert, B.A. Moffat, G.R. Reddy, P. McConville, D.E. Hall, T.L. Chenevert, M.S. Bhojani, S.M. Buck, A. Rehemtulla, Multifunctional nanoparticle platforms for in vivo MRI enhancement and photodynamic therapy of a rat brain cancer, J. Magn. Magn. Mater. 293 (2005) 404–410.
[15] V. Harihar Nath, S. Praveen, R.M. Chavan, Gold nanoparticle: synthesis and characterization, Vet. World 7 (2014) 72–77.
[16] K. Saha, S.S. Agasti, C. Kim, X. Li, V.M. Rotello, Gold nanoparticles in chemical and biological sensing, Chem. Rev. 112 (2012) 2739–2779.
[17] C. Li, D. Li, G. Wan, J. Xu, W. Hou, W, Facile synthesis of concentrated gold nanoparticles with low size-distribution in water: temperature and pH controls, Nanoscale Res. Lett. 6 (2011) 1–10.
[18] N. Hanžić, T. Jurkin, A. Maksimović, M. Gotić, The synthesis of gold nanoparticles by a citrate-radiolytical method, Radiat. Phys. Chem. 106 (2015) 77–82.
[19] R. Shenhar, T.B. Norsten, V.M. Rotello, Polymer-mediated nanoparticle assembly: structural control and applications, Adv. Mater. 17 (2005) 657–669.
[20] Y. Zhou, C.Y. Wang, Y.R. Zhu, Z.Y. Chen, A novel ultraviolet irradiation technique for shape-controlled synthesis of gold nanoparticles at room temperature, Chem. Mater. 11 (1999) 2310–2312.
[21] C.H. Walker, J.V. St.John, P. Wisian-Neilson, Synthesis and size control of gold nanoparticles stabilized by poly (methylphenylphosphazene). , J. Am. Chem. Soc. 123 (2001) 3846–3847.
[22] X. Wang, G. Li, T. Chen, M. Yang, Z. Zhang, T. Wu, H. Chen, Polymer-encapsulated gold-nanoparticle dimers: facile preparation and catalytical application in guided growth of dimeric ZnO-nanowires, Nano Lett. 8 (2008) 2643–2647.
[23] S. Guo, L. Wang, E. Wang, Templateless, surfactantless, simple electrochemical route to rapid synthesis of diameter-controlled 3D flowerlike gold microstructure with “clean” surface, Chem. Commun. 30 (2007) 3163–3165.

[24] J. Shan, H. Tenhu, Recent advances in polymer protected gold nanoparticles: synthesis, properties and applications, Chem. Commun. 44 (2007) 4580–4598.
[25] D.A. Giljohann, D.S. Seferos, P.C. Patel, J.E. Millstone, N.L. Rosi, C.A. Mirkin, Oligonucleotide loading determines cellular uptake of DNA-modified gold nanoparticles, Nano Lett. 12 (2007) 3818–3821.
[26] Z. Wang, A.G. Kanaras, A.D. Bates, R. Cosstick, M. Brust, Enzymatic DNA processing on gold nanoparticles, J. Mater. Chem. 14 (2004) 578–580.
[27] F. Kim, J.H. Song, P. Yang, Photochemical synthesis of gold nanorods, J. Am. Chem. Soc. 124 (2002) 14316–14317.
[28] Y. Zhou, C.Y. Wang, Y.R. Zhu, Z.Y. Chen, A novel ultraviolet irradiation technique for shape-controlled synthesis of gold nanoparticles at room temperature, Chem. Mater. 11 (1999) 2310–2312.
[29] T.K. Sau, A. Pal, N.R. Jana, Z.L. Wang, T. Pal, Size controlled synthesis of gold nanoparticles using photochemically prepared seed particles, J. Nanopart. Res 3 (2001) 257–261.
[30] Mdel Pilar Rodríguez-Torres, L.A. Díaz-Torres, S. Romero-Servin, Heparin Assisted Photochemical Synthesis of Gold Nanoparticles and Their Performance as SERS Substrates, Int. J. Mol. Sci. 15 (2014) 19239–19252.
[31] M. Grzelczak, L.M. Liz-Marzán, The relevance of light in the formation of colloidal metal nanoparticles, Chem. Soc. Rev. 4 (2014) 2089–2097.
[32] K. Okitsu, A. Yue, S. Tanabe, H. Matsumoto, Y. Yobiko, Formation of colloidal gold nanoparticles in an ultrasonic field: control of rate of gold (III) reduction and size of formed gold particles, Langmuir 17 (2001) 7717–7720.
[33] L.P. Jiang, S. Xu, J.M. Zhu, J.R. Zhang, J.J. Zhu, H.Y. Chen, Ultrasonic-assisted synthesis of monodisperse single-crystalline silver nanoplates and gold nanorings, Inorg Chem. 43 (2004) 5877–5883.
[34] J.P. Sylvestre, S. Poulin, A.V. Kabashin, E. Sacher, M. Meunier, J.H. Luong, Surface chemistry of gold nanoparticles produced by laser ablation in aqueous media. , J. Phys. Chem. B. 108 (2004) 16864–16869.
[35] F. Mafuné, J.Y. Kohno, Y. Takeda, T. Kondow, H. Sawabe, Formation of gold nanoparticles by laser ablation in aqueous solution of surfactant, J. Phys. Chem. B. 105 (2001) 5114–5120.
[36] A.E. Urusov, A.V. Petrakova, P.G. Kuzmin, A.V. Zherdev, P.G. Sveshnikov, G.A. Shafeev, B.B. Dzantiev, Application of gold nanoparticles produced by laser ablation for immunochromatographic assay labeling, Anal. Biochem. 491 (2015) 65–71.
[37] P. Matteini, F. Ratto, F. Rossi, S. Centi, L. Dei, R. Pini, Chitosan films doped with gold nanorods as laser-activatable hybrid bioadhesives, Adv. Mater. 22 (2010) 4313–4316.
[38] C. Loo, A. Lin, L. Hirsch, M.H. Lee, J. Barton, N. Halas, J. West, R. Drezek, Nanoshell-enabled photonics-based imaging and therapy of cancer, Technol. Cancer Res T 3 (2004) 33–40.
[39] U. Shedbalkar, R. Singh, S. Wadhwani, S. Gaidhani, B.A. Chopade, Microbial synthesis of gold nanoparticles: current status and future prospects, Adv. Colloid Interface Sci. 209 (2014) 40–48.
[40] K.N. Thakkar, S.S. Mhatre, R.Y. Parikh, Biological synthesis of metallic nanoparticles, Nanomed. Nanotechnol. Biol. Med. 6 (2010) 257–262.
[41] A.G. Kanaras, Z. Wang, A.D. Bates, R. Cosstick, M. Brust, Towards multistep nanostructure synthesis: programmed enzymatic self-assembly of DNA/gold systems, Angew. Chem. Int. Ed. 115 (2003) 201–204.
[42] H.M. Zakaria, A. Shah, M. Konieczny, J.A. Hoffmann, A.J. Nijdam, M.E. Reeves, Small molecule-and amino acid-induced aggregation of gold nanoparticles, Langmuir 2 (2013) 7661–7673.
[43] X. Liang, Z.J. Wang, C.J. Liu, Size-controlled synthesis of colloidal gold nanoparticles at room temperature under the influence of glow discharge, Nanoscale Res. Lett. 5 (2010) 124–129.
[44] P. Prema, P.A. Iniya, G. Immanuel, Microbial mediated synthesis, characterization, antibacterial and synergistic effect of gold nanoparticles using Klebsiella pneumoniae (MTCC-4030), RSC Adv. 6 (2016) 4601–4607.
[45] H. Barabadi, S. Honary, P. Ebrahimi, M.A. Mohammadi, A. Alizadeh, F. Naghibi, Microbial mediated preparation, characterization and optimization of gold nanoparticles, Braz. J. Microbiol. 45 (2014) 1493–1501.
[46] A. Ahmad, S. Senapati, M.I. Khan, R. Kumar, M. Sastry, Extracellular biosynthesis of monodisperse gold nanoparticles by a novel extremophilic actinomycete, Thermomonospora sp, Langmuir 19 (2003) 3550–3553.
[47] O. Habib, D.O. Demirkol, S. Timur, Sol–gel/chitosan/gold nanoparticle-modified electrode in mediated bacterial biosensor, Food Anal. Method. 5 (2012) 188–194.
[48] F. Ramezani, M. Ramezani, S. Talebi, Mechanistic aspects of biosynthesis of nanoparticles by several microbes, Nanocon 10 (2010) 1–7.
[49] H.Y. Kim, H.G. Song, Purification and characterization of NAD (P) H-dependent nitroreductase I from Klebsiella sp. C1 and enzymatic transformation of 2, 4, 6-trinitrotoluene, Appl. Microb. Biotechnol. 68 (2005) 766–773.
[50] F. Hollmann, A. Schmid, Electrochemical regeneration of oxidoreductases for cell-free biocatalytic redox reactions, Biocatal. Biotransformation. 22 (2004) 63–88.
[51] F. Ramezani, M. Ramezani, S. Talebi, Mechanistic aspects of biosynthesis of nanoparticles by several microbes, Nanocon 10 (2010) 1–7.
[52] Y.S. Park, Y.N. Hong, A. Weyers, Y.S. Kim, R.J. Linhardt, Polysaccharides and phytochemicals: a natural reservoir for the green synthesis of gold and silver nanoparticles, Nanobiotechnology, IET 5 (2011) 69–78.
[53] J.L. Gardea-Torresdey, J.G. Parsons, E. Gomez, J. Peralta-Videa, H.E. Troiani, P. Santiago, M.J. Yacaman, Formation and growth of Au nanoparticles inside live alfalfa plants, Nano Lett. 2 (2002) 397–401.
[54] N.C. Sharma, S.V. Sahi, S. Nath, J.G. Parsons, J.L. Gardea-Torresde, T. Pal, Synthesis of plant-mediated gold nanoparticles and catalytic role of biomatrix-embedded nanomaterials. , Environ. Sci. Technol. 41 (2007) 5137–5142.
[55] A. Gangula, R. Podila, L. Karanam, C. Janardhana, A.M. Rao, Catalytic reduction of 4-nitrophenol using biogenic gold and silver nanoparticles derived from Breynia rhamnoides, Langmuir 27 (2011) 15268–15274.
[56] A.S. Reddy, C.Y. Chen, C.C. Chen, J.S. Jean, H.R. Chen, M.J. Tseng, C.W. Fan, J.C. Wang, Biological synthesis of gold and silver nanoparticles mediated by the bacteria Bacillus subtilis, J. Nanosci. Nanotechnol. 10 (2010) 6567–6574.
[57] M.I. Husseiny, M. Abd El-Aziz, Y. Badr, M.A. Mahmoud, Biosynthesis of gold nanoparticles using Pseudomonas aeruginosa, Spectrochim. Acta Mol. Biomol. Spectrosc. 67 (2007) 1003–1006.
[58] L. Du, J. Hong, L. Xiaohua, W. Erkang, Biosynthesis of gold nanoparticles assisted by Escherichia coli DH5α and its application on direct electrochemistry of hemoglobin, Electrochem Commun. 9 (2007) 1165–1170.
[59] H. Shiying, G. Zhirui, Y. Zhang, S. Zhang, J. Wang, G. Ning, Biosynthesis of gold nanoparticles using the bacteria Rhodopseudomonas capsulata, Mater. Lett. 61 (2007) 3984–3987.
[60] Y. Nangia, W. Nishima, G. Nisha, G. Shekhawat, C. Raman Suri, A novel bacterial isolate Stenotrophomonas maltophilia as living factory for synthesis of gold nanoparticles, Microb. Cell Fact. 8 (2009) 39–46.
[61] K. Kalishwaralal, D. Venkataraman, R. Suresh Babu, K. Muniasamy, S. BarathManiKanth, K. Bose, G. Sangiliyandi, Biosynthesis of silver and gold nanoparticles using Brevibacterium casei, Colloids Surf. B. 77 (2010) 257–262.
[62] K. Kalishwaralal, V. Deepak, S.R.K. Pandian, S. Gurunathan, Biological synthesis of gold nanocubes from Bacillus licheniformis, Bioresour. Technol. 100 (2009) 5356–5358.
[63] S. Baker, S. Satish, Biosynthesis of gold nanoparticles by Pseudomonas veronii AS41G inhabiting Annona squamosa L, Spectrochim. Acta Part A: Mol. Biomol. Spectrosc. 15 (2015) 691–695.
[64] C. Malarkodi, S. Rajeshkumar, M. Vanaja, K. Paulkuman, G. Gnanajobitha, G. Annadurai, Eco-friendly synthesis and characterization of gold nanoparticles using Klebsiella pneumoniae, J. Nanostruct. Chem. 3 (2013) 1–7.
[65] A.K. Nishat Sharma, M. Raje, F.N. Ashish, M.S. Bhattacharyya, A.R. Choudhury, Exploitation of marine bacteria for production of gold nanoparticles, Microb. Cell Fact. 11 (2012) 86.
[66] D.N. Correa-Llantén, S.A. Muñoz-Ibacache, M.E. Castro, P.A. Muñoz, J.M. Blamey, Gold nanoparticles synthesized by Geobacillus sp. strain ID17 a thermophilic bacterium isolated from Deception Island, Antarctica, Microb. Cell Fact. 12 (2013) 1–6.
[67] P. Mukherjee, S. Senapati, D. Mandal, A. Ahmad, M.I. Khan, R. Kumar, M. Sastry, Extracellular synthesis of gold nanoparticles by the fungus Fusarium

oxysporum, Chem. Biol. Chem. 3 (2002) 461–463.
[68] S.K. Das, C. Dickinson, F. Lafir, D.F. Brougham, E. Marsili, Synthesis, characterization and catalytic activity of gold nanoparticles biosynthesized with Rhizopus oryzae protein extract, Green. Chem. 14 (2012) 1322–1334.
[69] T. Ogi, N. Saitoh, T. Nomura, Y. Konishi, Room-temperature synthesis of gold nanoparticles and nanoplates using Shewanella algae cell extract, J. Nanopart. Res. 12 (2010) 2531–2539.
[70] G. Singaravelu, J.S. Arockiamary, V.G. Kumar, K. Govindaraju, A novel extracellular synthesis of monodisperse gold nanoparticles using marine alga, Sargassum wightii Greville, Colloids Surf. B: Biointerfaces 57 (2007) 97–101.
[71] J. Xie, J.Y. Lee, D.I. Wang, Y.P. Ting, Identification of active biomolecules in the high-yield synthesis of single-crystalline gold nanoplates in algal solutions, Small 3 (2007) 672–682.
[72] S.P. Chandran, M. Chaudhary, R. Pasricha, A. Ahmad, M. Sastry, Synthesis of gold nanotriangles and silver nanoparticles using Aloevera plant extract, Biotechnol. Adv. 22 (2006) 577–583.
[73] V.G. Kumar, S.D. Gokavarapu, A. Rajeswari, T.S. Dhas, V. Karthick, Z. Kapadia, T. Shrestha, I.A. Barathy, A. Roy, S. Sinha, Facile green synthesis of gold nanoparticles using leaf extract of antidiabetic potent Cassia auriculata, Colloids Surf. B. 87 (2011) 159–163.
[74] D. Philip, Green synthesis of gold and silver nanoparticles using Hibiscus rosa sinensis, Phys. E Low Dimens. Syst. Nanostruct. 42 (2010) 1417–1424.
[75] M.R. Bindhu, M. Umadevi, Antibacterial activities of green synthesized gold nanoparticles, Funct. Mater. Lett. 120 (2014) 122–125.
[76] V. Kumar, S.K. Yadav, Plant-mediated synthesis of silver and gold nanoparticles and their applications, J. Chem. Technol. Biotechnol. 84 (2009) 151–157.
[77] W. Wang, Q. Chen, C. Jiang, D. Yang, X. Liu, S. Xu, One-step synthesis of biocompatible gold nanoparticles using gallic acid in the presence of poly-(N-vinyl-2-pyrrolidone), Colloid Surf. A. 301 (2007) 73–79.
[78] R.G. Pearson, Hard and soft acids and bases, J. Am. Chem. Soc. 85 (1963) 3533–3539.
[79] A. Kumar, S. Mandal, P.R. Selvakannan, R. Pasricha, A.B. Mandale, M. Sastry, Investigation into the interaction between surface-bound alkylamines and gold nanoparticles, Langmuir 19 (2003) 6277–6282.
[80] J.Y. Song, H.K. Jang, B.S. Kim, Biological synthesis of gold nanoparticles using Magnolia kobus and Diopyros kaki leaf extracts, Process Biochem. 44 (2009) 1133–1138.
[81] V. Armendariz, I. Herrera, M. Jose-yacaman, H. Troiani, P. Santiago, J.L. Gardea-Torresdey, Size controlled gold nanoparticle formation by Avena sativa biomass: use of plants in nanobiotechnology, J. Nanopart. Res. 6 (2004) 377–382.
[82] T. Elavazhagan, K.D. Arunachalam, Memecylon edule leaf extract mediated green synthesis of silver and gold nanoparticles, Int. J. Nanomed. 6 (2011) 1265–1278.
[83] E.E. Connor, J. Mwamuka, A. Gole, C.J. Murphy, M.D. Wyatt, Gold nanoparticles are taken up by human cells but do not cause acute cytotoxicity, Small 1 (2005) 325–327.
[84] P. Rajasekharreddy, P.U. Rani, B. Sreedhar, Qualitative assessment of silver and gold nanoparticle synthesis in various plants: a photobiological approach, J. Nanopart. Res. 12 (2010) 1711–1721.
[85] D. Philip, C. Unni, Extracellular biosynthesis of gold and silver nanoparticles using Krishna tulsi (Ocimum sanctum) leaf, Phys. E Low. Dimens Syst. Nanostruct. 43 (2011) 1318–1322.
[86] J.Y. Song, H.K. Jang, B.S. Kim, Biological synthesis of gold nanoparticles using Magnolia kobus and Diopyros kaki leaf extracts, Process Biochem. 44 (2009) 1133–1138.
[87] D. MubarakAli, N. Thajuddin, K. Jeganathan, M. Gunasekaran, Plant extract mediated synthesis of silver and gold nanoparticles and its antibacterial activity against clinically isolated pathogens, Colloids Surf. B. 85 (2011) 360–365.
[88] S.R. Bonde, D.P. Rathod, A.P. Ingle, R.B. Ade, A.K. Gade, M.K. Rai, Murraya koenigii-mediated synthesis of silver nanoparticles and its activity against three human pathogenic bacteria, Nanosci. Methods 1 (2012) 25–36.
[89] L. Zecca, M.B. Youdim, P. Riederer, J.R. Connor, R.R. Crichton, Iron, brain ageing and neurodegenerative disorders, Nat. Rev. Neurosci. 5 (2004) 863–873.
[90] M.V. Sujitha, S. Kannan, Green synthesis of gold nanoparticles using Citrus fruits (Citrus limon, Citrus reticulata and Citrus sinensis) aqueous extract and its characterization, Spectrochim. Acta A Mol. Biomol. Spectrosc. 102 (2013) 15–23.
[91] B. Ankamwar, C. Damle, A. Ahmad, M. Sastry, Biosynthesis of gold and silver nanoparticles using Emblica officinalis fruit extract, their phase transfer and transmetallation in an organic solution, J. Nanosci. Nanotechnol. 5 (2005) 1665–1671.
[92] G.S. Ghodake, N.G. Deshpande, Y.P. Lee, E.S. Jin, Pear fruit extract-assisted room-temperature biosynthesis of gold nanoplates, Colloids Surf. B Biointerfaces 75 (2010) 584–589.
[93] D. Preeti, M. Mausumi, Prunus domestica fruit extract-mediated synthesis of gold nanoparticles and its catalytic activity for 4-nitrophenol reduction, Ind. Eng. Chem. Res. 51 (2012) 13014–13020.
[94] P. Daisy, K. Saipriya, Biochemical analysis of Cassia fistula aqueous extract and phytochemically synthesized gold nanoparticles as hypoglycemic treatment for diabetes mellitus, Int. J. Nanomed. 7 (2012) 1189.
[95] A. Gangula, R. Podila, L. Karanam, C. Janardhana, A.M. Rao, Catalytic reduction of 4-nitrophenol using biogenic gold and silver nanoparticles derived from Breynia rhamnoides, Langmuir 27 (2011) 15268–15274.
[96] N. Roy, R.A. Laskar, I. Sk, D. Kumari, T. Ghosh, N.A. Begum, A detailed study on the antioxidant activity of the stem bark of Dalbergia sissoo Roxb, an Indian medicinal plant, Food Chem. 126 (2011) 1115–1121.
[97] J. Pérez-Jiménez, V. Neveu, F. Vos, A. Scalbert, Identification of the 100 richest dietary sources of polyphenols: an application of the Phenol-Explorer database, Eur. J. Clin. Nutr. 1 (2010) 12–20.
[98] A. Ebrahimi, H. Schluesener, Natural polyphenols against neurodegenerative disorders: potentials and pitfalls, Ageing Res. Rev. 30 (11) (2012) 329–345.
[99] C. Jayaseelan, R. Ramkumar, A.A. Rahuman, P. Perumal, Green synthesis of gold nanoparticles using seed aqueous extract of Abelmoschus esculentus and its antifungal activity, Ind. Crops Prod. 28 (2013) 423–429.
[100] J. Hernandez, J. Solla-Gullon, E. Herrero, Gold nanoparticles synthesized in a water-in-oil microemulsion: electrochemical characterization and effect of the surface structure on the oxygen reduction reaction, J. Electroanal. Chem. 574 (2004) 185–196.
[101] E.C. Da Silva, M.G. Da Silva, S.M. Meneghetti, G. Machado, M.A. Alencar, J.M. Hickmann, M.R. Meneghetti, Synthesis of colloids based on gold nanoparticles dispersed in castor oil, J. Nanopart. Res. 10 (2008) 201–208.
[102] C.M. Niemeyer, The developments of semisynthetic DNA–protein conjugates, Trends Biotechnol. 20 (2002) 395–401.
[103] J.M. Slocik, M.O. Stone, R.R. Naik, Synthesis of gold nanoparticles using multifunctional peptides, Small 1 (2005) 1048–1052.
[104] Y. Li, Z. Tang, P.N. Prasad, M.R. Knecht, M.T. Swihart, Peptide-mediated synthesis of gold nanoparticles: effects of peptide sequence and nature of binding on physicochemical properties, Nanoscale 6 (2014) 3165–3172.
[105] C.M. Niemeyer, B. Ceyhan, DNA-directed functionalization of colloidal gold with proteins, Angew. Chem. Int. Ed. 40 (2001) 3685–3688.
[106] J. Liu, Y. Lu, Preparation of aptamer-linked gold nanoparticle purple aggregates for colorimetric sensing of analytes, Nat. Protoc. 1 (2006) 246.