Journal of Trace Elements in Medicine and Biology 40 (2017) 10–23

Contents lists available at ScienceDirect

Journal of Trace Elements in Medicine and Biology

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

Review

# Recent advances in plant-mediated engineered gold nanoparticles and their application in biological system

Khwaja Salahuddin Siddiqi[a], Azamal Husen[b,*]

[a] Department of Chemistry, Aligarh Muslim University, Aligarh 202002, Uttar Pradesh, India
[b] Department of Biology, College of Natural and Computational Sciences, University of Gondar, P.O. Box #196, Gondar, Ethiopia

ARTICLE INFO

*Article history:*
Received 20 May 2016
Received in revised form 9 October 2016
Accepted 22 November 2016

*Keywords:*
Gold nanoparticles
Green synthesis
Plant extract
Reaction mechanism
Anticancer

ABSTRACT

For biosynthesis of gold nanoparticles different parts of a plant are used as they contain metabolites such as alkaloids, flavonoids, phenols, terpenoids, alcohols, sugars and proteins which act as reducing agents to produce nanoparticles. They also act as capping agent and stabilizer for them. They are used in medicine, agriculture and many other technologies. The attention is therefore focussed on all plant species which have either aroma or colour in their leaves, flowers or roots for the synthesis of nanoparticles because they all contain such chemicals which reduce the metal ions to metal nanoparticles. The size and morphology of gold nanoparticles is dependent on the biogenic-synthetic route, incubation time, temperature, concentration and pH of the solution. In this review, we have discussed the latest developments for the fabrication of gold nanoparticles from herbal extract, their characterization by UV–vis., Fourier transform infrared spectroscopy, transmission electron microscopy, scanning electron microscopy, X-ray diffraction, atomic force microscopy, energy-dispersive X-ray spectroscopy, dynamic light scattering and Zeta Potential techniques. Their application in drug delivery, cancer treatment, catalysis and as antimicrobial agent has also been discussed.



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* Corresponding author.
*E-mail address:* adroot92@yahoo.co.in (A. Husen).

http://dx.doi.org/10.1016/j.jtemb.2016.11.012
0946-672X/

## 1. Introduction

Gold is a precious coinage metal used in jewellery and other artefacts from ancient times [1,2]. It is a soft, dense and bright yellow metal which is resistant to oxidation by air and moisture and generally unaffected by mild acids. The gold nanoparticles are biocompatible with large surface area and high dispersion owing to their very small size. The synthesis, characterization and their use in biology, medicine and agriculture has produced significant results [3–5]. Plant-mediated synthesis of metal nanoparticles has become very popular due to ease and availability of plant material which contain reducing compounds such as sugars, proteins, phenols, amines, ketones, aldehydes, carboxylic acids etc. [6–8]. However, several contradictory results of the use of gold nanomaterials on plant growth and development have been reported [4]. They can effectively bind to amine and thiol groups which help in surface modification and increase their effectiveness in biomedical applications [9]. They are commercially used as rapid testing arrays for pregnancy, biomolecule detectors, DNA labelling, drug delivery, immunostaining, catalytic activity, biosensors and in environmental monitoring [9–16]. Since gold nanoparticles are non-toxic and readily adsorb DNA they are also used for bombardment in the delivery of genetic materials into plants [17] in quantitative determination of heavy metals [18] blood glucose [19] and pesticides [20].

Antimicrobial activity of gold nanoparticles has also been reported in the preceding years by many workers [21–25]. The functions of gold nanoparticle are shape and size dependent. For instance, the gold nano rods are excellent biosensors and used as hyperthermia agent to kill cancer cells [26,27]. They have been employed in the thermal degradation of cancer cells and drug delivery [28,29]. The nano bubbles containing gold nanoparticles are injected in the body of the cancer patient and their movement is monitored. The moment they reach the affected area a laser beam or infra red rays are applied to raise the temperature, as a consequence of which the nano bubbles burst and the gold nanoparticles are released. Thus, the normal healthy cells are prevented from the interaction of nanoparticles. The gold nanoparticles adhere to the cancer cell wall and slowly penetrate into them inhibiting their further growth. The process is popularly known as Golden Bullet Technique.

Synthesis of gold nanoparticles of well-defined shape and size depends on the concentration of plant extract/biomass, metal salt, pH of the reaction mixture, temperature and incubation time. Biogenic fabrication of gold nanoparticles using various plants and their parts are summarized in Table 1.

This review article concentrates on some recent advances in green-synthetic techniques to produce gold nanoparticles, their characterization by UV–vis, FTIR spectroscopy, transmission electron microscopy (TEM), scanning electron microscopy (SEM), X-ray diffraction (XRD), atomic force microscopy (AFM), energy-dispersive X-ray spectroscopy (EDX), dynamic light scattering (DLS), zeta potential and their applications in cutting-edge areas.

## 2. Factors responsible for gold nanoparticle fabrication

It has been noticed that the plants and their parts which have aroma or colour, contain amino acids, enzymes, flavonoids, aldehydes, ketones, amines, carboxylic acids, phenols, proteins and alkaloids as reducing agents which convert the gold ion to gold nanoparticles. Thus, for biosynthesis, one must always select a plant which contains at least one of the above mentioned chemicals which reduces the metal ion to elemental metal. Rate of gold nanoparticles fabrication and their stability is an important aspect in industrial production. Thus, the influence of reaction conditions should be properly monitored. The gold nanoparticles fabricated from plant extract vary in shape and size (Table 1 and Fig. 1). Morphology of gold nanoparticles depends on the pH, temperature, incubation time, concentration of plant extract and that of the metal salt (Table 2).

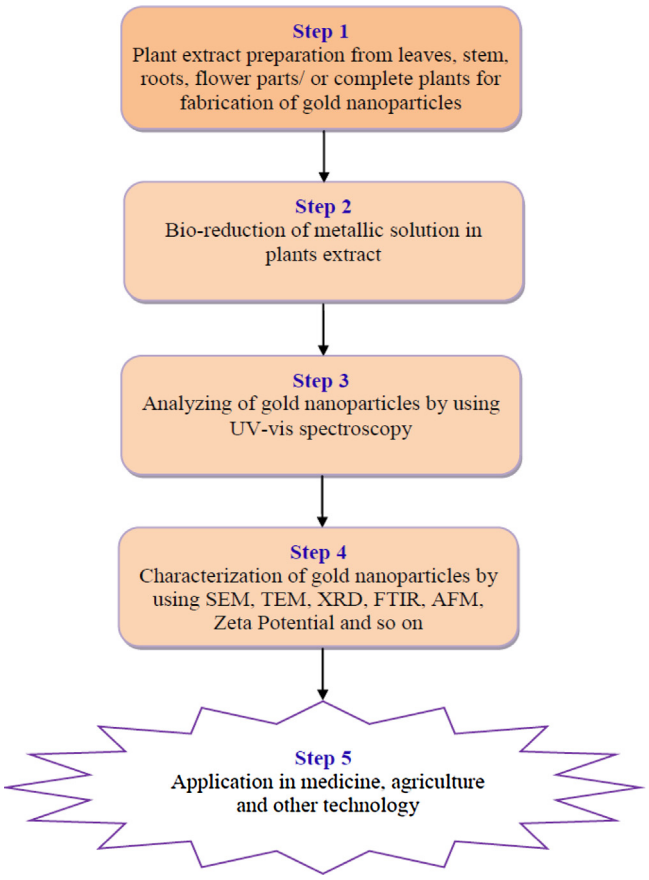


**Fig. 1.** Fabrication of gold nanoparticles from plant extract and their characterization.

## 3. Gold nanoparticles fabrication and their characterization

Usually plant-mediated gold nanoparticles are characterized by UV–vis, FTIR spectroscopy, SEM, TEM, EDX and XRD analyses. UV–vis. spectroscopy in 500–550 nm region is used in characterizing the gold nanoparticles [50]. For instance, gold nanoparticles fabricated from aqueous seed extract of *Abelmoschus esculentus* showed (Fig. 2a) an absorption peak at 536 nm [92]. The FTIR spectra of gold nanoparticles (Fig. 2b) and aqueous seed extract of *A. esculentus* (Fig. 2c) showed the presence of alcohol, proteins and aromatic amines which act as reducing agents. The OH groups have been suggested to act as capping agent for the nanoparticles.

Gold nanoparticles have been fabricated using live *Madicago sativa* by gold ion uptake from solid media [92]. Nanoparticles of different structures (face centred cubic, tetrahedral, hexagonal, decahedral, icosahedral and irregular rod-shaped) are produced from *Avena sativa* biomass [87]. The yield was found to be higher at pH 3, while at higher pH, the smaller size of nanoparticles were obtained. In this study, the rod shaped nanoparticles were obtained at all pH which have been reported to be formed mainly by electrodeposition. $KAuCl_4$ was used as the source which on dissolution in water gives $AuCl_4^-$ anion. They are bonded to carboxylic groups which are already protonated at low pH. The *A. sativa* biomass exhibited the capacity to bind $AuCl_4^-$ and its successive reduction to gold nanoparticles. Chandarn et al. [33] have reported the syn-

**Table 1**
Gold nanoparticle as fabricated from different parts of a plant with their size and shape.

| Key references | Plant | Part used | Size (nm) | Shape |
|---|---|---|---|---|
| [30] | *Acacia nilotica* | Leaves | 6–12 | Spherical |
| [31] | *Aegle marmelos* | Leaves | 38.2 ± 10.5 | Spherical |
| [32] | *Aerva lanata* | Leaves | 17.97 | – |
| [33] | *Aloe vera* | Leaves | – | Crystalline |
| [34] | *Angelica archangelica* | Root | 3–4 | Spherical, ovals, polyhedral |
| [35] | *Antigonon leptopus* | Leaves | 13–28 | Spherical, triangular |
| [36] | *Azadirachta indica* | Leaves | 5.5–7.5 | Crystalline |
| [37] | *Beta vulgaris* | Sugar beet pulp | | Spherical, rod-shaped nanowires |
| [38] | *Brassica juncea* | Leaves | 10–20 | Near spherical |
| [39] | *Cacumen platycladi* | Leaves | 2.2–42.8 | Face-centred cubic (fcc) crystalline |
| [40] | *Camellia sinensis* | Leaves (tea bag) | 40 | Spherical, triangular, irregular |
| [41] | *Cassia tora* | Leaves | 41 | – |
| [42] | *Chenopodium album* | Leaves | 10–30 | Quasi-spherical |
| [43] | *Cicer arietinum* | Bean | – | Triangular |
| [44] | *Cinnamomum camphora* | Leaves | 80, 23.4, 21.5 | Spherical, triangular |
| [45] | *Cinnamomum zeylanicum* | Leaves | 25 | Spherical, prism |
| [46] | *Coleus amboinicus* | Leaves | 4.6–55.1 | Spherical, triangular, truncated, triangular, hexagonal, decahedral |
| [47] | *Coriandrum sativum* | Leaves | 6.7–57.9 | Spherical, triangular, turnacated, decahedral |
| [48] | *Commelina nudiflora* | Plant | 20–80 | Spherical, truncated, triangular |
| [49] | *Cuminum cyminum* | Seed | 1–10 | Spherical |
| [50] | *Cymbopogon flexuosus* | Leaf | 12–30 | Triangular |
| [51] | *Diopyros kaki* | Leaves | 5–300 | Spherical, triangular, pentagonal, hexagonal |
| [52] | *Emblica officinalis* | Fruit | 15–25 | – |
| [36] | *Eucalyptus camaldulensis* | Leaves | 5.5–7.5 | Crystalline |
| [53] | *Euphorbia hirta* | Leaves | 6–71 | Spherical |
| [54] | *Ficus racemosa* | Latex | 20–50 | – |
| [34] | *Hypericum perforatum* | Bark | 4–6 | Spherical, polyhedral |
| [34] | *Hamamelis virginiana* | Bark | 4–6 | Spherical, polyhedral |
| [55] | *Jasminum nervosum* | Leaves | 2–20 | Spherical |
| [56] | *Madhuca longifolia* | Leaves | – | Triangular, spherical, hexagonal nanoplates |
| [51] | *Magnolia kobus* | Leaves | 5–300 | Spherical, triangular, pentagonal, hexagonal |
| [57] | *Mangifera indica* | Leaves | 17–20 | Spherical |
| [58] | *Memecylon edule* | Leaves | 10–45 | Circular, triangular, hexagonal |
| [59] | *Menta piperita* | Laves | 150 | Spherical |
| [60] | *Momordica charantia* | Fruit | 500–600 | – |
| [61] | *Morinda citrifolia* | Root | 12.17–38.26 | Cubic |
| [62] | *Moringa oleifera* | Petals | 3–5 | Hexagonal, triangular |
| [63] | *Murraya koenigii* | Leaves | 20 | Spherical, triangular |
| [64] | *Nigella sativa* | Essential oil | 15.6–28.4 | Spherical |
| [65] | *Nyctanthes arbortristis* | Flower | 19.8 | Spherical, triangular, hexagonal |
| [66] | *Pelargonium graveolens* | Leaves | 20–40 | Decahedral, icosahedral |
| [36] | *Pelargonium roseum* | Leaves | 5.5–7.5 | Crystalline |
| [67] | *Pistacia integerrima* | Gall | 20–200 | – |
| [68] | *Psidium guajava* | Leaves | 25–30 | Spherical |
| [69] | *Punica granatum* | Juice | 23–36 | Triangular, pentagonal, hexagonal, spherical |
| [70] | *Rosa hybrida* | Petal | ~10 | Spherical, triangular, hexagonal |
| [71] | *Rosa rugosa* | Leaves | 11 | Triangular and hexagonal |
| [72] | *Salix alba* | Leaves | 50–80 | – |
| [73] | *Sesbania drummondii* | Seed | 6–20 | Spherical |
| [74] | *Sphaeranthus amaranthoides* | Leaves | 39 | Spherical |
| [75] | *Stachys lavandulifolia* | Plant | 34–80 | Spherical, triangular |
| [76] | *Stevia rebaudiana* | Leaves | 8–20 | Octahedral |
| [77] | *Stevia rebaudiana* | Leaves | 5–20 | Spherical |
| [25] | *Salicornia brachiata* | Plant | 22–35 | Spherical |
| [78] | Sargentodoxa cuneata | Plant | 15–30 | Hexagonal |
| [79] | *Tanacetum vulgare* | Fruit | 11 | Triangular |
| [80] | *Terminalia catappa* | Leaves | 10–35 | Spherical |
| [81] | *Terminalia arjuna* | Fruit | 20–50 | Spherical |
| [82] | *Terminalia arjuna* | Bark | 15–20 | Triangular, tetragonal, pentagonal, hexagonal, rod-like, spherical |
| [83] | *Trigonella foenum-graecum* | Seeds | 15–25 | Spherical |
| [84] | *Urtica dioica* | Leaves | 1–195 | Small spheres, large triangles |
| [85] | *Vitis vinifera* | Leaves | 18–25 | Triangular, pentagonal, spherical |
| [86] | *Zingiber officinale* | Roots | 5–15 | Spherical |

thesis of gold nanoparticles with spherical and triangular shape and a variety of sizes using *Aloe vera* plant extract. They have demonstrated that only biomolecules of less than 3 kDa in weights are responsible for reduction of gold ions to gold nanotriangles. Stable gold nanoparticles were produced from *Coriandrum sativum* leaf extract at room temperature [47]. They were spherical, triangular, truncated and decahedral in morphologies ranging from 6.7 to 57.9 nm in size.

*Magnolia kobus* and *Diopyros kaki* were used for extracellular gold nanoparticles production [51]. Nearly 90% conversion was achieved at 95 °C. They were ~5–300 nm in size with triangular, pentagonal, hexagonal and spherical shapes. Song et al. [51] proposed that the speed of nanoparticles synthesis was proportional related to temperature. However, by increasing temperature and leaf broth concentration, smaller gold nanoparticles were obtained. FTIR spectra of gold nanoparticles and *M. kobus* extract showed the presence of biomolecules such as proteins and terpenoids hav-

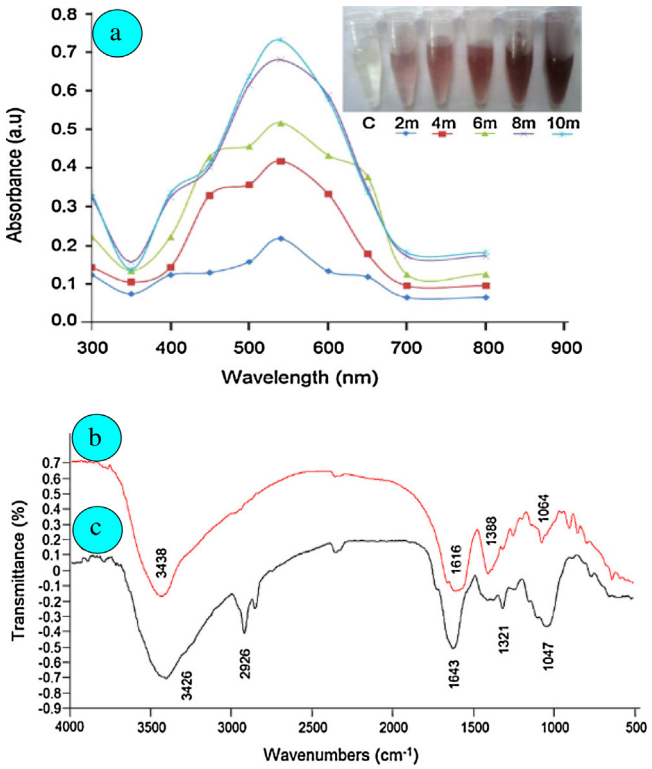


**Fig. 2.** **(a)** UV–vis spectroscopy of synthesized gold nanoparticles using seed aqueous extract of *Abelmoschus esculentus* showed peak at 536 nm; FTIR spectrum of **(b)** synthesized gold nanoparticles and **(c)** aqueous seed extract of *Abelmoschus esculentus* [adopted from [92]].

ing amines, aldehydes, carboxylic acids and alcohols as functional groups.

Gold nanoparticles obtained from *Gnidia glauca* flower extract has shown a remarkable chemocatalytic activity in the reduction of 4-nitrophenol to 4-aminophenol in the presence of sodium borohydride [89]. At concentration as low as 0.7 mM, the synthesis was optimum, while above this concentration, the formation of nanoparticles ceases to continue. The yield of nanoparticles increases with increasing temperature and attains maximum between 40 °C and 50 °C. Morphologically, they were nanotriangles to nanohexagons, majority being spherical and the particle size range between 50 and 150 nm. It was interesting to note that the gold nanoparticles fabrication was started after 2 min interaction with flower extract with $HAuCl_4$.

Sadeghi et al. [77] have reported the fabrication of gold nanoparticles from dried leaf extract of *Stevia rebaudiana* in aqueous medium. TEM and SEM images showed average sizes of the gold nanoparticles of 5–20 nm. Their FTIR spectra showed that they were functionalized with biomolecules containing primary amine group ($-NH_2$), carbonyl group, —OH groups and other stabilizing functional groups. It was found from XRD study that NP of 17 nm had face centred cubic structure. They have found, from zeta potential measurement that these gold nanoparticles were stable in a wide range of pH (6–12).

It has been reported that the aqueous fruit extract of *Terminalia arjuna* contains tannin, terpenoid, saponins, flavonoids, glycosides and polyphenols [81]. AFM (Fig. 3) and TEM studies showed that gold nanoparticles of 20–50 nm were spherical in shape. DLS study [93] suggested that they were in the range of 5–60 nm and average size was 25 nm. However, some large particles were also found due to agglomeration.

Ahmed et al. [25] have synthesized gold nanoparticles from aqueous extract of *Salicornia brachiata* and studied their catalytic

**Table 2**
Effect of pH, temperature and incubation time of the solution on the shapes of gold nanoparticles.

| Key references | Level | Shapes |
|---|---|---|
| [37] | pH 9 | Spherical |
| [37] | pH 10 | Rod shaped |
| [37] | pH 11 | Nanowires |
| [87] | pH 2 | Larger, rod shaped |
| [87] | pH 3–4 | Smaller, rod shaped |
| [34] | pH 8 | Spherical, oval, polygedral |
| [51] | 25 °C | Triangular |
| [51] | 60 °C | Pentagonal |
| [51] | 90 °C | Hexagonal |
| [88] | 40 °C | Spherical |
| [89] | 50 °C | Spherical, nanoprisms, nanotriangles, hexagons trapezoids |
| [33] | 5 h | Spherical |
| [33] | 25 h | Triangular |
| [47] | 12 h | Spherical, triangular, turnacated, decahedral |
| [63] | 2 min | Smaller, spherical |
| [65] | 2.5 h | Spherical |
| [90] | 3 min | Spherical |
| [88] | 30 min | Spherical |
| [89] | 20 min | Spherical, nanoprisms, nanotriangles, hexagons trapezoids |
| [91] | 6 min | Spherical |

and antibacterial activity against *Escherichia coli*, *Pseudomonas areuoginosa*, *Salmonella typhii* and *Staphylococcus aureus*. The nanoparticles exhibited purple colour with a characteristic surface plasmon resonance (SPR) at 532 nm. SEM and TEM confirmed polydispersed nature of gold nanoparticles of 22–35 nm size. They were pure and crystalline. It is surprising that the nanoparticles were not formed even when a mixture of $HAuCl_4$ and plant extract was heated to 60 °C in sunlight. However, the reaction was catalysed by the addition of trace amount of 10 μm potassium borohydride and shear change in colour was observed within 5 min which did not diminish even after 30 days. These gold nanoparticles were investigated for their catalytic activity for reduction of nitrophenol and methylene blue. The reduction of 4-nitrophenol to 4-aminophenol was followed by UV–vis spectrum that was accompanied by a change in colour from yellowish-green to colourless. Reduction of methylene blue to leucomethylene blue by gold nanoparticles in presence of $NaBH_4$, was indicated by loss in colour [94,95]. Initially aqueous methylene blue showed two absorption peaks at 664 and 614 nm which disappeared after reduction. The antibacterial activity of gold nanoparticles, ofloxacin and a combination of nanoparticles with ofloxacin was investigated. It is important to note that the combined activity of gold nanoparticle mixed with ofloxacin was much higher than either the nanoparticles or antibiotic alone. A more effective biocompatible mixture of a suitable antibiotic and gold nanoparticle may therefore be produced to prevent crops from damage by pathogens.

Majumdar et al. [30] have reported the controlled synthesis of gold nanoparticles from *Acacia nilotica* leaf extract, and their catalytic activity at room temperature, without any additional stabilizing agent.

$$\text{Polyphenol} + Au^{3+} \rightarrow \text{Polyquinone} + Au^0$$

These workers have suggested that $Au^0$ thus formed collide with each other to form gold nanoparticles. It must be made clear that $Au^0$ in elemental form are, in fact, gold nanoparticles. There is no further variation in their size. All atoms of gold are equal in dimension and stay in colloidal form. The change in colour is mainly due to variation in shape which is reflected from absorption peaks at 533 nm and 529 nm in visible region of the spectra. The other absorption peaks are due to the oxidation of phenol and amines in the leaf extract [96]. Majumdar et al. [30] have also reported

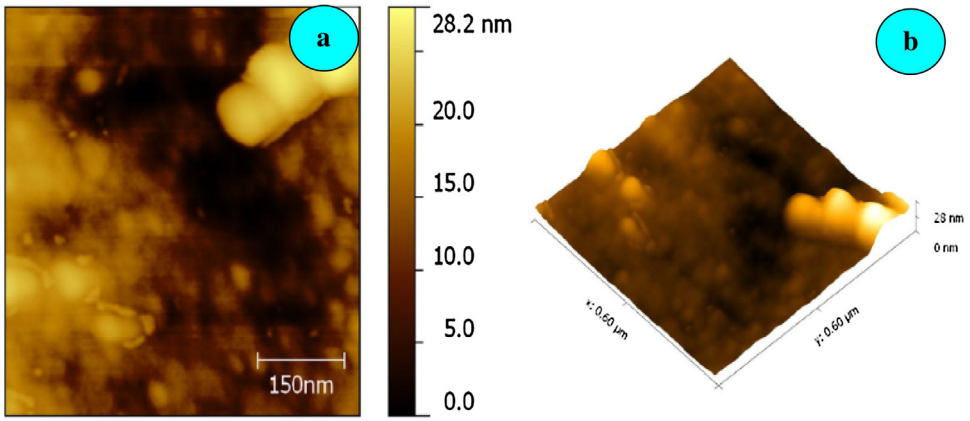


**Fig. 3.** AFM micrographs of synthesized gold nanoparticles from the aqueous fruit extract of *Terminalia arjuna* **(a)** 2D image and **(b)** 3D image [adopted from [81]].

gold nanoparticles of 6–12 nm size at room temperature. The catalytic reduction of 4-nitorphenol by gold nanoparticles in presence of potassium borohydride has been demonstrated spectrophotometrically by the appearance of peak at 400 nm with increased intensity.

Mishra et al. [91] have fabricated water soluble well dispersed gold nanoparticles from leaf and stem extract of *Hibiscus sabdariffa*. Higher amount of gold nanoparticles was obtained between pH 4–6 (in acidic condition) at 100 °C within less time (~6 min). To know the chemical state of the gold nanoparticles, X-ray photoelectron spectroscopy (XPS) analysis was also carried out. The Au 4f7/2 spectrum had two peaks at 81.0 and 84.5 eV, corresponding to the binding energies of metallic gold ($Au^0$) and gold ions ($Au^{n+}$).

Salunke et al. [97] have reported the synthesis of 20–30 nm gold nanospheres from the root extract of *Plumbago zeylanica* and characterized them by UV–vis, IR spectra, XRD, EDS, TEM, HPTLC and GCMS. The gold nanoparticles adhere to form gold nano triangles. They also exhibited antimicrobial and antibiofilm activity against *Escherichia coli*, *Acinetobacter baumannii* and *Staphylococcus aureus*. It was observed that the nanoparticles formation is accelerated with increasing temperature and concentration of salt with a maximum of 50 °C temperature and 0.7 mM concentration. The TEM images showed some noteworthy features of gold nanoparticles. They were anisotropic with spheres, triangles and hexagons (Fig. 4a, b). They showed significantly higher antimicrobial activity relative to those synthesized chemically. It appears as if the shape, diffusion and organic contents from the root extract also enhance their activity.

Arunachalam et al. [98] have reported one pot biosynthesis and characterization of gold and silver nanoparticles from leaf extract of *Memecylon umbellatum*. The plant is known to contain saponins, phenols, phytosterols and quinones which help in bioredcution of gold and silver ions. Their antimicrobial activity against several bacteria has been evaluated. The TEM images showed the formation of spherical, hexagonal and triangular gold nanoparticles. They were monodispersed with an average size of 17 nm. The energy dispersive X-ray (EDAX) analysis showed gold signals at 2.3, 8.1, 9.4 and 11.3 keV (Fig. 5).

Gold nanoparticles have been synthesized from *Cucurbita pepo* plant extract at 40 °C [88]. It was noted that shoot extract yielded large number of gold nanoparticles (spherical) than the root extract of plant because different parts of the plants contain different amounts of reducing agents. It is essential that the green synthesis uses environment friendly solvent, eco-friendly reducing agent and non toxic stabilizing agent. These strategies may prevent atmospheric pollution. In the present case the reduction of $HAuCl_4$ was done at 40 °C for 30 min with shoot extract of plant exhibiting an absorption peak at about 570 nm. Any variation in this absorption may be due to the variation in the quantity of reductant. The dynamic light scattering (DLS) analysis showed that about 93% gold nanoparticles are of approximately 627 nm.

Biogenic synthesis of gold nanoparticle has also been done using rose petals [70]. The reaction was completed within 5 min which suggests that rose petals contain fairly large quantity of reducing agents. They also act as stabilizers for nanoparticles. The average particle size was found to be 10 nm. Their synthesis has also been reported from *Aegle marmelos* leaf extract [31]. It is a one step process that yields spherical nanoparticles of ~38.2 ± 10.5 nm. They have also been used for the detection of thiamine but the process has been overemphasized.

It has been reported that gold nanoparticles of 4–8 nm diameter of various shapes were produced at room temperature at pH 8 from *Angelica archangelica*, *Hypericum perforatum*, *Hamamelis virginiana* plant extracts [34]. They were characterized by UV–vis, FTIR spectroscopy, TEM and AFM images. The electronic spectrum of gold nanoparticles exhibited absorption bands at about 520–540 nm due to SPR. The aggregation of nanoparticles causes a broadening of the absorption band and a bathochromic shift of the maxima toward over 600 nm. It has been suggested that nanoparticles are stabilized by the reduction products of the organic compounds present in plants such as quinone. They are spherical, oval or polyhedral in shape. The nanoparticles undergo self agglomeration at pH 5, which may be prevented by raising the pH to 8.

*Ficus racemosa* latex was used as a reducing agent for the synthesis of gold and silver nanoparticles [54]. The colloidal solutions of the nanoparticles showed characteristic absorption peaks in their UV–vis spectra. It has been suggested that under acidic condition, COOH and amine groups of amino acids bind with nanoparticles but under basic conditions the $COO^-$ and $NH_2$ of the same acids can not bind the nanoparticles. It is very strange obsession of Tetgure et al. [54], that they have hypothesized such imaginary chemical binding of nanoparticles with amino acids under acidic condition.First, the nanoparticles are neutral atoms which can associate themselves under both acidic and basic conditions. Second, only two charged species may be bonded together such as a metal ion and a ligand forming donor acceptor complex. It seems that the authors have mistaken the agglomeration with complexation. It is not surprising that aggregation of neutral atoms such as Helium, Neon and Argon and, molecules such as methane are aggregated due to very weak force like van der Waals forces.

Recently, an enzymatic digestion method was developed, for simultaneous determination of gold nanoparticle size, distribution, particle concentration and dissolved gold concentration in tomato plant tissues [99]. The results suggested that tomato plants can

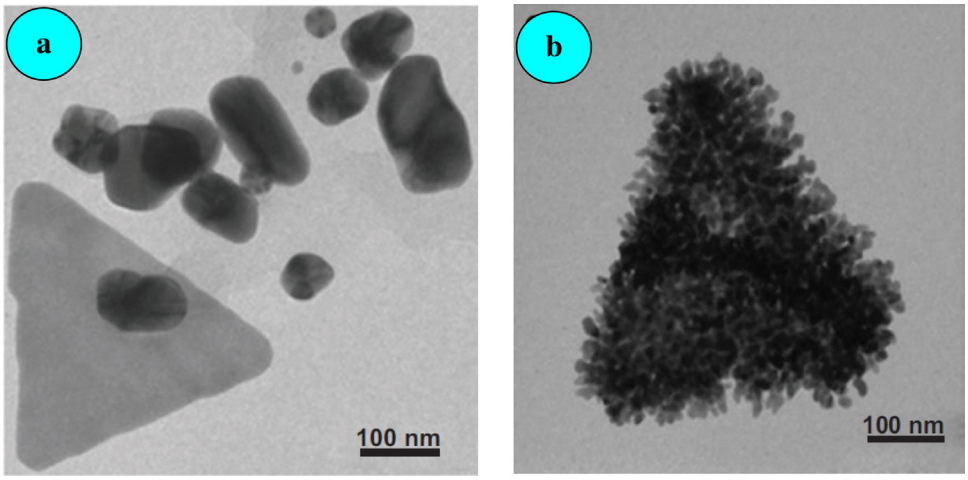


**Fig. 4.** Characterization of nanoparticles synthesized by *Plumbago zeylanica* root extract using transmission electron microscopy **(a)** shape evolution of gold nanotriangles and **(b)** assembly of gold nanospheres forming a gold nanotriangle [adopted from [98]].

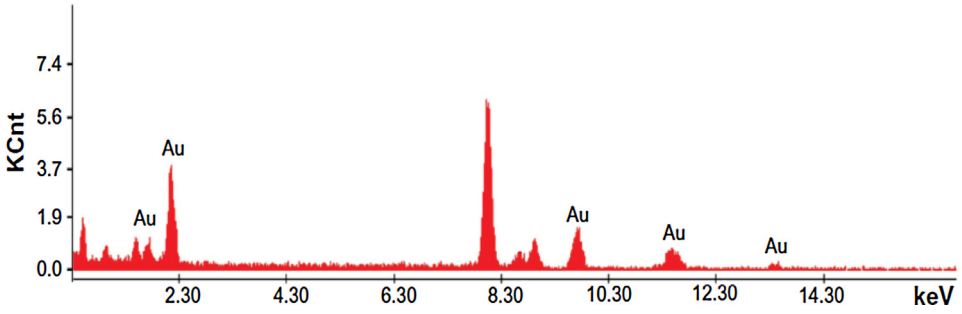


**Fig. 5.** Energy dispersive X-ray spectrum of gold nanoparticles from leaf extract of *Memecylon umbellatum* [adopted from [99]].

uptake gold nanoparticles of 40 nm diameter and transport them to various parts of the plant. Authors have suggested that Macerozyme R-10 enzyme can be used to extract gold nanoparticles from the plant tissues.

Antibiotics coupled with inorganic nanoparticles have higher antibacterial properties. If the bacteria or pathogenic fungi are resistant to antibiotics they may be killed by metal nanoparticles without influencing the biocompatibility of antibiotics. Gu et al. [100] have shown enhanced activity of vancomycin coated gold nanoparticles on vancomycin resistant enterococci. Rai et al. [22] have reported one pot synthesis of spherical gold nanoparticles of 22–52 nm with a cofactor in a temperature range between 20 and 70 °C. As the temperature increases the particle size decreases with a consequent lowering of the absorption band from 540 nm to 532 nm. The cofactor containing amine group can protonate in acidic or neutral medium and reduce gold ions [101–104] to gold nanoparticles. They are also synthesized and capped by cofactor (Scheme 1) [102]. The shape and size of nanoparticles is temperature dependent. Antimicrobial activity of cofactor reduced gold nanoparticle has been found to be greater than those of gold nanoparticles or cofactor alone. They were further coated with polymer, such as poly(ethyleneimine) for their biomedical application. It is very encouraging to note that such gold nanoparticles retain their activity under most acidic and most basic conditions (pH 3 – pH 10) and inhibit growth of *Escherichia coli* and *Staphylococcus aureus*. They inhibit the synthesis of peptidoglycan layer producing hole in bacterial cell wall, resulting in the leakage of cell material leading to their death.

Gold nanoparticles synthesized from leaf extract of *Cassia tora* were characterized by zeta sizer, TEM and FTIR [41]. The synthesized gold nanoparticles of *C. tora* secondary metabolites conjugate exhibited enhanced bioavailability, antioxidant and anticancer effect against colon cancer cell line (Col320). Gold nanoparticles were prepared by adding aqueous plant extract of *Nepenthes khasiana* to gold chloride solution [105]. It was observed that at 40 °C yield was high. Authors have suggested that they are suitable for in vivo biomedical applications via direct intravenous route. It has been suggested that gold nanoparticles produce colour from red to dark purple depending upon the size and shape. The red colour indicates smaller particles with mostly spherical shape, whereas purple colour exhibits larger particle size with mixed morphology. Gold nanoparticles fabricated from aqueous plant extract of *N. khasiana*, exhibit purple colour which was confirmed by the appearance of a peak at 570 nm in UV–vis spectrum. The influence of pH was also examined in gold nanoparticles fabrication. Purple colour was found at neutral pH (7), florescent purple colour at alkaline pH (10) and no colour in acidic pH (2). Authors claimed that the gold nanoparticles from *N. khasiana are* obtained only at neutral pH, whereas Ghodake et al. [106] have reported that the alkaline condition served as a high yielding medium. Perhaps, the presence of alkaline responsive plant metabolites present in pear fruit act as reducing agents only in alkaline medium. Thus, the presence of various types of metabolites in plants also plays an essential role in exploiting the medium for gold nanoparticle fabrication.

*Antigonon leptopus* leaf extract was used for fabrication and characterization of gold nanoparticles. They exhibited growth inhibitory property at the concentration ($GI_{50}$) of 257.8 $\mu g\,mL^{-1}$ in human adenocarcinoma breast cancer (Michigan Cancer Foundation – 7) cells after 48 h [35]. They may be used as a source for the development of anticancer drug in future. Manju et al. [64] produced gold nanoparticles from *Nigella sativa* oil which are able to control the growth and biofilm formation of Gram positive

*Staphylococcus aureus* than Gram negative *Vibrio harveyi*. Anticancer activity against human lung cancer has been also recorded. In this study, XRD analysis showed the presence of crystalline gold nanoparticle with distinctive facets (111, 200, 220 and 311 planes) which was also reported in earlier studies [61,107]. FTIR spectrum has shown the presence of amide linkage and some proteins in the reaction mixture were responsible for nanoparticles formation and their stabilization.

Gold nanoparticles were fabricated from a mixture of leaf extracts of *Carica papaya* and *Catharanthus roseus* [108]. It has been suggested that they change colour from yellow to ruby red which is their characteristic feature and also exhibit SPR band between 500 and 600 nm region. In a recent communication Islam et al. [67] have reported the synthesis and biological activity of gold nanoparticles of 20–200 nm size from the gall extract of *Pistacia integerrima*. The amines, amide and alcohol present in the plant extract act as capping and reducing agents. The formation of nanoparticles may be followed by measuring absorption of colour change from pink to ruby red with an absorption maximum at 536 nm in UV–vis spectrum. These nanoparticles are thermally stable up to 80 °C and at slight variation in pH. They have also studied the enzyme inhibiting properties of gold nanoparticles against urease, xanthine oxidase and carbonic anhydrase besides their antimicrobial activity against three bacteria and antifungal activity against three common fungi but the effect is almost negligible.

## 4. Application of gold nanoparticle

From the ancient civilization gold nanoparticles have been used to treat diseases such as smallpox, skin ulcers, syphilis and measles [109–114]. Currently, gold nanoparticles have attracted more attention due to their unique optical and electrical properties, high stability and good biocompatibility. Further, the recent developments in the synthesis and surface functionalization of gold nanoparticles have shown promising applications in cutting-edge areas (Fig. 6). Before exploiting the potential of gold nanoparticles it is also essential to consider the clinical efficiency and toxicological issues. Since the gold nanoparticles are knowingly introduced into the body system for treatment they may interact with diseased cells and healthy cell equally [115,116]. However gold is not considered as hazard when used as food additives [117] but many other nanoparticles inhaled inadvertently may produce adverse effect on body parts. Although gold nanoparticles are taken up by human tissues they do not cause acute toxicity [118]. Although gold is biologically inert and has low clearance rate from circulation, the cumulative deposition may lead to health issues if substantial quantity is retained in the body. Over 90% of intravenously injected gold nanoparticles may remain circulating in the system for about a week and a fraction of it may accumulate in the liver [119]. Such accumulation however, is not acute even after repeated administration of gold nanoparticles [120]. Small gold nanoparticles have shown to cause concentration dependent hemolysis in vitro [121]. Mammal (rabbits) administrated with gold nanoparticles did not show acute toxicity within 24 h nor there occur any change in specific affect [122]. However, toxicity experiments in dogs using gold nanoparticles showed transient weight loss which was recovered within 37 days without producing any abnormality in blood. Some black pigments were observed after 10 months which is suspected to be due to gold accumulation in the Kupffer cells in the liver, in the red pulp of the spleen and in the lymph nodes [123].

### 4.1. Gold nanoparticles in medicine and biology

Although many nanoparticles have been thoroughly investigated for biomedical application targeting cancer, gold nanoparticles have been employed both as a drug for cancer treatment as well as drug carrier. Since the nanoparticles are several thousand folds smaller than the living cells, proteins and enzymes; they are capable of penetrating into cancer cells to prevent their replication. Facile tunable size and functionality of gold nanoparticles makes them useful in drug delivery system. Gold nanoparticles [124] are used for cancer diagnosis and treatment both in vitro and in vivo. They are used in immunoassay [125], protein assay and electrophoresis [126]. They have also been successfully used in the delivery of peptides, proteins or nucleic acids like DNA or RNA [127–131]. They were also used as a carrier in the preparation of the anticancer agent, paclitaxel [132] and attached with vascular endothelial growth factor antibodies which are employed in treating B-chronic lymphocytic leukemia [133]. Gold nanoparticles conjugated oligonucleotide/DNA were used in clinical diagnosis and colourimetric detection of targeted DNA [134–136] and virus etc. [137–139]. The DNA template self assembly of gold nanoparticles has been employed to fabricate new biomaterials. Very recently, Dharanivasan et al. [140] reported the gold nanoparticles-bifunctional oligonucleotide probe conjugate for detection of dsDNA even in very minute quantity.

Surface-enhanced Raman spectroscopy (SERS) by gold nanoparticles are used in the identification of tumors [141], cancer cell targeting and traceable intracellular drug delivery [142], immunoassays [143,144] study of living cells [145], detection of Alzheimer's disease markers [146], protease activity [147] and many other activities [9]. Biological compounds and biomolecules adhere to the surface of gold nanoparticles through metal ligand, M ⟵ L bond and the bond between them is partly [148] covalent. Gold as $Au^{3+}$ ion has greater affinity to sulphur containing ligands than nitrogen or oxygen [157] but functionalized gold nanoparticles provide stronger binding between them. The polymer coated or protein functionalized gold nanoparticle present zwitterionic conditions providing cationic to anionic sites which us related to the change of pH from basic to acidic. This is the key to identification and can be switched from cationic ↔ anion by irritation. The efficiency of the process depends on the shape and size of the gold nanoparticles. Release of the molecules from gold nanoparticle can be controlled by heating and the gold conjugate by pulsed laser excitation [149].

Gold nanoshells have also been checked for drug delivery. Composites of hydrogels and nanoshells have been developed for photochemically modulated drug delivery [150]. When it was irradiated at 1064 nm the nanoshells absorbed the radiation and converted it to thermal energy which was enough to burst the hydrogel releasing the drug. Thus the drug can be delivered at the target cell without interacting with the normal cells. Hyperthermia by photoinduced heating of gold nanoparticles will work for tissues close to skin if irradiation is done with IR light. For tissues deeper in the body, heating with magnetic particles is more favourable. The hollow gold nanoparticles can encapsulate small molecules such as horse radish peroxidase enzyme which retains its activity inside the nanoshell. It has also been observed that this enzyme trapped in solid gold nanoparticles did not show any activity. The gold nanoparticles can easily penetrate into leaky tumor vasculature than in normal healthy tissues. For drug delivery by gold nanoparticle it is essential that they should be apparently larger to encapsulate the drug. The smaller nanoparticles (<10 nm) are not ideal as drug carrier [11]. The drug delivery through gold nanoparticles follows absorption of the drug on the surface of nanoparticles and subsequent insertion of the whole conjugate into the cell (Fig. 7). The penetration may be triggered by gene gun simply by insertion of nanoparticle-conjugate. Inside the cells the drug molecules are detached from the gold nanoparticles and are probably attached to the protein molecules inside the cancer cells [151,152]. The colloidal gold nanoparticles carry the drug to the site

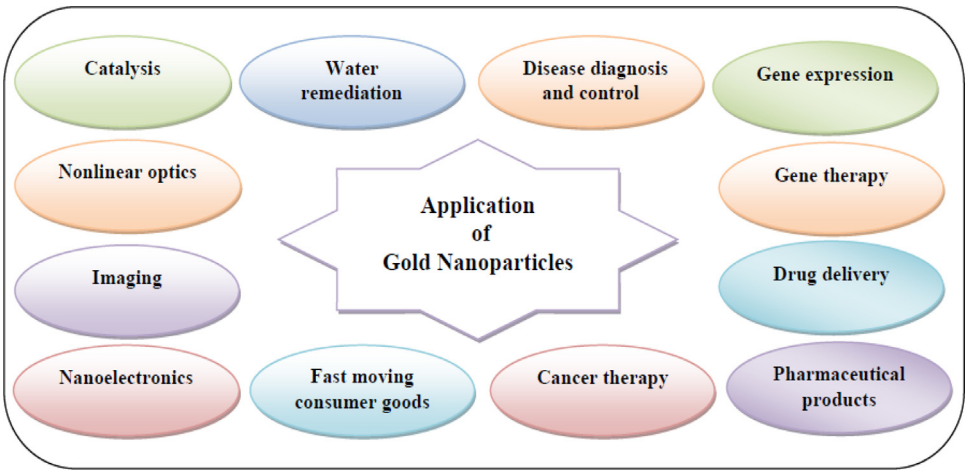


**Fig. 6.** Application of gold nanoparticles in cutting-edge areas.

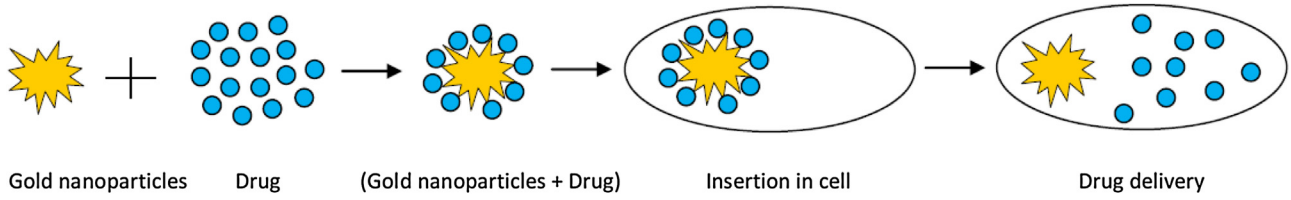


**Fig. 7.** Possible mechanism of drug delivery using gold nanoparticles on the target cells.

of use irrespective of their shape provided both of them are biocompatible, stable and easily form bond with gold. The nanoparticles are finally deposited in cells and on irradiation with visible light the heat mediated by gold nanoparticles destroys the cancerous tissues locally [27,153,154]. Rana et al. [142] have also studied the delivery of drugs, genetic materials, proteins and small molecules through gold nanoparticle. They have also shown the efficiency and decreased toxicity of gold nanoparticle coated with polymers such as poly(ethylene glycol). Conjugation of gold nanoparticle with folic acid using PEG as spacer provided selective delivery to specific cells [155,156].

A combined photothermal therapy with SERS for cancer detection has been proposed by Wu et al. [157]. They prepared gold–silver bimetallic nanoparticles (100–120 nm) functionalized with the S2.2 aptamer to target MUC1 receptors on MCF-7 breast cancer cells. The nanoparticles were surrounded by a gold shell which inhibits silver toxicity and the combination of gold and silver in the core enabled SERS of the Raman reporter Rh6G for MCF-7 cell detection. Targeting studies showed increased nanoparticle uptake by cells (MCF-7) while little binding to liver cancer cells (HEPG2) or breast cancer cells (MCF-10A). Further, low power laser irradiation (808 nm, 0.06–0.25 W/cm$^2$, 60 min) of these bimetallic particles resulted in 97% breast cancer cell death without destroying the healthy cells and the surrounding normal tissue. Cancer cells in real-time was studied in situ to understand changes in cellular morphology that occur during photothermal heating [159]. Gold nanorods were functionalized with the negatively charged polyelectrolyte polystyrenesulfonate to increase nanorod biocompatibility. EMT-6 breast cancer cells were incubated for overnight with gold nanorods to facilitate uptake into the endosomes or lysosomes. Endocytosis resulted in the uptake of a few hundred to a few thousand nanorods per cell. Irradiation with a femtosecond pulsed laser (790 nm, 0.5 ms) seemed to explode the lysosomes in the cells; however the cell death was not quick. Further, photothermal treatment caused damage of cell due to the formation of 10 μM cavities and then led to rupture of the plasma membrane. Subsequent intracellular responses eventually resulted in cells death within 4 min of laser irradiation at 185 and 222 W/cm$^2$ (Fig. 8). Chen et al. [158] concluded that cell death was mainly the result of oncosis (ischemic cell death) due to sudden swelling. In addition, results of this investigation offers significant inspection towards evaluating and improving the performance of gold nanorods based photothermal therapy.

### 4.2. Gold nanoparticles as signal producers/biosensors

Change in colour of gold nanoparticle has been used as biosensor to detect DNA/RNA, proteins and metal ions [159–162]. Usually, well dispersed gold nanoparticle solution is red but turns blue when they aggregate. This pattern of aggregation is associated with the recognition of biomolecules followed by colour change which can be visualized even with naked eye [163]. Gold nanoparticle in elemental form can be dissolved to produce gold ions through a redox process which can be detected by electrochemical methods. Electrochemical biosensors have therefore, been developed to detect infectious diseases [164]/and pathogens. It is based on the binding of the cationic surface of gold ions and the anionic surface of pathogens such as *Escherichia coli*.

Gold nanoparticles are used as biosensors in recognition of elements [165]. It has been found that the gold nanoparticles are used in medical devices in enormously high quantity (540 kg in UK, 2700 kg in USA) and therefore their disposal is also high. It is essential to convert them to useful compounds to prevent the environment from adverse effects. Gold nanoparticle have been used in chemical sensing of potassium [166], lithium [167] and other toxic heavy metals like mercury, lead and cadmium [168]. They are also useful for the removal of heavy metals by the formation of alloys with varying composition, for example $Au_3Hg$, AuHg, $AuHg_3$ phases, and thus they can be utilized for the removal of Hg ions from contaminated water [169]. Dang et al. [170] have reported a sensor for the selective detection of $Cr^{3+}$ in aqueous solution, in the presence of 15 other metal ions. Gold nanoparticle can also be used for the detection and removal of organic compounds such as pesticides

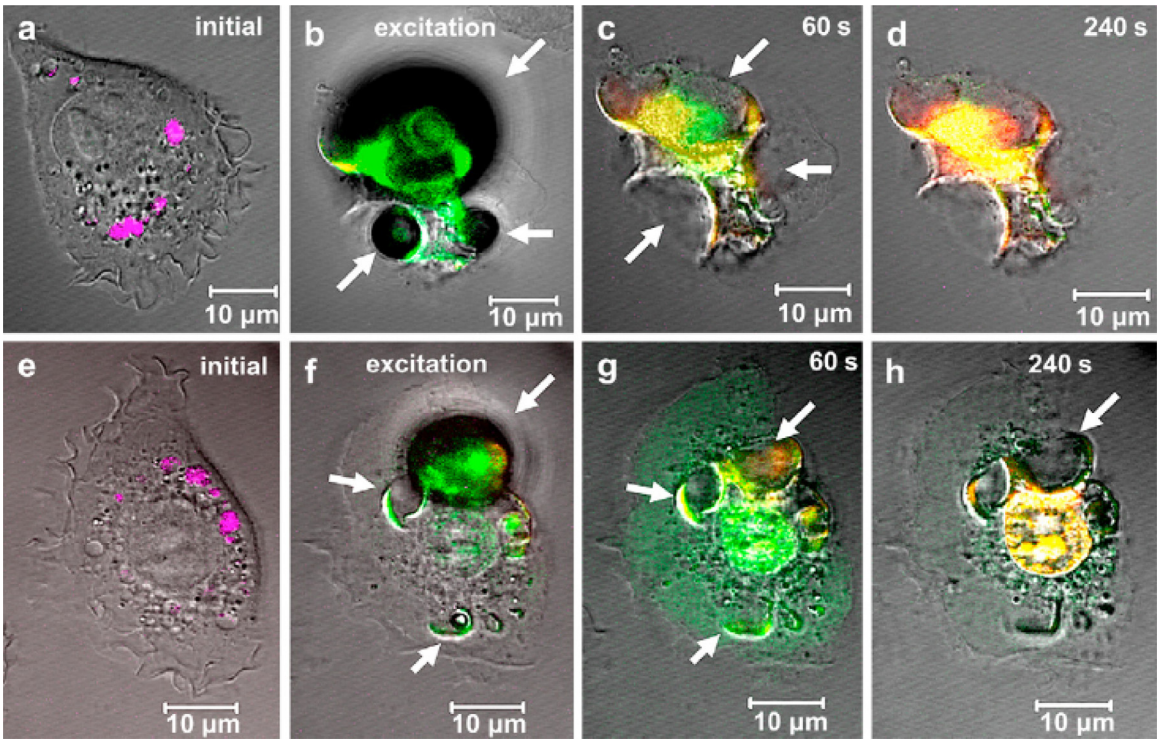


**Fig. 8.** Photothermolysis of the EMT-6 tumor cell triggered by gold nanorods under different energy fluences. (a–d) 113 mJ/cm$^2$; (e–h) 93 mJ/cm$^2$. Location of gold nanorods was observed using two-photon photoluminescence and is indicated by the purple dots but disappears after irradiation due to gold nanorod melting. Green stain exhibits increased cell membrane permeability and red stain (propidium iodide) is indicative of cell death. Arrows indicates the formation of characteristic cavities due to photothermal damage [adopted from [160]]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

[171] endosulfan, malathion and chlorpyrifos [172]. Bootharaju and Pradeep [173] have reported the decomposition of chlorpyrifos at room temperature in presence of gold nanoparticles. Salt-induced aggregation of gold nanoparticles was also used for the detection of pesticides in drinking water at low concentration [174]. Removal of diesel oil droplets floating on water through swelling and absorption of the gold nanoparticle composite have also been determined [175]. They have also been utilized in the biosensor designing to improve the performance for the detection of infectious diseases [163].

### 4.3. Gold nanoparticles as antimicrobial agents

Gold nanoparticles have shown antimicrobial properties [4,5]. Functionalized gold nanoparticles have been found to effectively reduce the growth of Gram-negative and Gram-positive bacteria [176]. Silver and gold nanoparticles obtained from *Mentha piperita* have exhibited a strong antibacterial activity against *Staphylococcus aureus* and *Escherichia coli* [59]. Antibacterial activities of honey-mediated gold and silver nanoparticles have also been observed [23]. Very recently, green synthesis of gold nanoparticles from aqueous extract of *Brassica oleracea* has been done [177]. Nanoparticles appeared after 30 min incubation of $HAuCl_4$ with broccoli under ambient conditions. The change in colour was noted with an absorption maximum at 560 nm in the UV–vis region. SEM micrograph showed average size ranging between 12 and 22 nm. These gold nanoparticles have been shown to be growth inhibitors of bacteria, *Staphylococcus aureus*, *Klebsiella pneumonia* and fungi, *Aspergillus flavus*, *Aspergillus niger* and *Candida albicans*. Their antimicrobial efficiency is comparable with standard Gentamicin and Fluconazole. Thus, they may also be used in place of antibiotics.

### 4.4. Gold nanoparticles as catalyst

Gold nanoparticles are used as catalyst for selective reactions at low temperature such as the water gas shift reaction and selective oxidation of carbon monoxide [178–180], methanol [181], glycerol [182], hydrogenation of unsaturated materials [183] reduction of aromatic nitro compounds [184] and a toxic pollutant 4-nitrophenol to 4-aminophenol [89,185]. Gopinath et al. [186] reported the biosyntheses of varying size of gold nanoparticles from fruit extract of *Tribulus terrestris*. An anisotropic structure of gold nanoparticles with average size of 7 nm and 55 nm were obtained. They exhibited size dependent activity against multidrug resistant *Helicobacter pylori* strains. These gold nanoparticles also showed catalytic reduction of *p*-nitroaniline to *p*-phenylenediamine.

### 4.5. Gold nanoparticles as antioxidants

Natural antioxidants prevent DNA damage, malignant transformation, cell damage, heart diseases, cancer and also oxidative stress [187]. Synthetic antioxidants are suspected to cause negative health effects [188]. Medhe et al. [189] have investigated the DPPH and OH radical scavenging activity of gold embedded 3,6-dihydroxyflavone. Radical scavenging activity of gold embedded 3,6-dihydroxyflavone alone and also in combination with dietary components such as lutein and selenium methyl selenocysteine has been determined. The combination of gold nanoparticles embedded flavones with other dietary nutrients showed considerable increase in antioxidant activity. Antioxidant-functionalized gold nanoparticles, Au@Trolox, synthesized from Trolox (vitamin E analogue, α-tocopherol) has been investigation for radical scavenging activity [190]. It showed that the rate constant for the reaction of Au@Trolox with DPPH (2,2-diphenyl-1-picrylhydrazyl) was nearly 8 times higher [191,192] than that of Trolox at all concentration. The present analysis revealed that quinonoid and the diepoxide

forms were possible oxidised products of the chromanol group of Au@Trolox treated with DPPH radical. It is suggested that instead of modifying the functional groups of antioxidant (tocopherol in this case) another ligand Trolox-SH be conjugated with gold nanoparticles. The results clearly demonstrate that introduction of gold nanoparticles enhances the radical scavenging efficiency without disturbing the antioxidant capacity of Trolox group. The antioxidant activity of $Au@SC_6H_{12}OH$ is inhibited because capped thiol monolayer shields the surface of gold core. Thus, new compounds with improved antioxidant activity may be developed by alkyl substitution at ortho or meta position of a phenolic hydroxyl moiety [193] and substitution of a heteroatom (N, S, Se) of oxygen of a chromanol ring [194–196]. Gold nanoparticles, epigallocatechin gallate (EGCG) and α-lipoic acid (ALA) has been shown to posses antioxidative properties and therefore, they have been used in the wound healing [197]. A combination of EGCG + ALA and gold nanoparticles + EGCG + ALA separately showed increased Hs68 and HaCat proliferation and migration application of the above mixture containing gold nanoparticle accelerated wound healing on mouse skin. Also it showed an increase Cu/Zn superoxide dismutase around the wound followed by decrease in CD68 protein expression through anti-inflammatory and antioxidizing properties. It is therefore, firmly believed that antioxidizing ability of known antioxidant, in conjugation with gold nanoparticles may be increased and can be successfully used in wound healing. The variation of size of gold nanoparticle did not significantly change the cell proliferation in the cell lines in vitro. It was found that a mixture of (EGCG + ALA) with gold nanoparticles was more effective in promoting the proliferation and migration of dermal fibroblast or keratinocytes than EGCG or ALA alone. This mixture can therefore, be effectively used in the restoration of normal dermal and epidermal tissues and in the treatment of injury [198] and skin wounds. A mixture of EGCG + ALA has shown increased antioxidant activity but when it spiked with gold nanoparticles the antioxidant ability is further enhanced, perhaps due to absorption of this mixture through the skin, both in vitro and in vivo.

### 4.6. Gold nanoparticles as photochemical agents

Citrate capped gold nanoparticles of 15, 30, 40 nm were synthesized and characterized by DLS and TEM [199]. Their size and dose dependent cytogenetic effects were studied against *Allium cepa* bioassay. The root tips of the plant were exposed to 0.1, 1.0 and 10 $\mu g\,mL^{-1}$ of 15, 30, 40 nm gold nanoparticles. Several chromosomal aberrations were observed, which increase with increasing concentration of gold nanoparticles. Koo et al. [200] have studied the uptake of gold nanoparticles through *Arabidopsis thaliana* roots and subsequent translocation to leaves. They have demonstrated the generation of nanobubbles and acoustic signals in the plants. It has also been demonstrated that leaves containing gold nanoparticles when exposed to laser beam, showed elevated temperature across the leaf surface and induced expression of heat-shock regulated genes. It is clear from the above results that gold nanoparticles in the leaves can act as photochemical agents and raise their temperature by absorption of light waves to induce photochemical activity even when the temperature is very low.

### 4.7. Gold nanoparticles in plant growth and production

Gold nanoparticles have demonstrated a significant promising potential for plant growth and production. They have shown beneficial as well as harmful impacts in plant system [4,201]. Gold nanoparticles enter into plant system by a size-dependent mechanism where they may trigger the growth/biomass or inhibit the growth. It has been reported that the metallic gold with zero nutritive value does not cause toxicity/growth inhibition but higher concentrations of gold solutions may cause toxicity, affect plant growth negatively [73,202–204] and may produce changes at physiological, biochemical and molecular levels [88,202,205–207]. The dose dependent effect of $KAuCl_4$ on primary root length of *Arabidopsis* seedlings have been investigated [206]. Root treatment with lower concentration (10 ppm $KAuCl_4$) triggered a significant increase in length while at higher concentration (25, 50 and 100 ppm) a significant decrease recorded. This study suggests low dose of $KAuCl_4$ stimulates the root growth whereas higher doses inhibit it. In addition, at higher doses iron is depleted and an increase in Zn and P contents was obtained. As a consequence of decrease in iron content in root tips and increase in monodispersed gold nanoparticle, an increase in iron responsive genes are triggered [206]. In *Arabidopsis thaliana,* gold nanoparticles have shown a significant role in seed germination, antioxidant system and altered levels of micro RNAs expression that regulates different morphological, physiological and metabolic processes [208]. It has been suggested that the gold nanoparticles may be applied in fruiting plants to increase the quality and quantity of the fruits and vegetable [201].

## 5. Conclusions and future research prospects

The gold nanoparticles of a variety of shape and size can easily be fabricated from herbal and plant extracts and also from fungi and bacteria in eco-friendly manner. These extracts are known to influence the characteristics of the gold nanoparticles since their composition varies from species to species and, accordingly different extracts contain different quantities of organic reducing agents. Thus, gold nanoparticles of various geometrical shape and size may be obtained from different types of plant and microbes. They are used in many diverse areas of medicine, agriculture and technology to improve the quality of life. Some of the current global issues such as clean potable water, sustainable energy and increased crop yield bank on the production of inexpensive and benign nano materials and their understanding at the molecular level. We still need to look for the potential and structure- activity relationship of nano materials for their use in future.

## Competing interests

The authors declare that they have no competing interests.

## Acknowledgment

Authors are thankful to publishers/authors for permission to adopt figures in this review.

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