International Journal of Multidisciplinary Trends

E-ISSN: 2709-9369
P-ISSN: 2709-9350
www.multisubjectjournal.com
IJMT 2022; 4(1): 274-278
Received: 05-04-2022
Accepted: 09-05-2022

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Analysis involved in the green synthesis of gold nanoparticle for biomedical application

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Abstract
Gold nanoparticle is an auspicious candidate for biomedical application because of their versatile physicochemical properties. Among different methods of preparation, green synthesis is one of the most promising approaches in the preparation of gold nanoparticles (AuNPs). Researchers are attracted towards this process because of its ability to produce eco-friendly, cost-effective, and biocompatible AuNPs which are more effective for biomedical applications. This short communication highlights the green synthesis and analytical methods used for the characterization of AuNPs. Characterizations such as Scanning electron microscopy (SEM) and Transmission electron microscopy (TEM) are performed for surface morphology analysis, X-ray diffraction (XRD) for crystallinity, Fourier transform infrared spectroscopy (FTIR) for functional groups, etc. Those green synthesized nanoparticles are widely used in the medical field and contain properties such as, antioxidant, anticancer, and anti-inflammatory and they have also proven as good candidates for drug delivery.

Keywords: Green synthesis, gold nanoparticles biocompatibility SEM, TEM, XRD

Introduction

Inorganic nanoparticles are nanoscale materials that exhibit distinct physical and chemical properties. Those nanoparticles display unique characteristics like chemical stability, high catalytic activity, magnetic property, optical, and electronic property, low dielectric constant etc [1]. because of their unique features, their application has been flourishing in energy storage, catalysis, and biomedical imaging like magnetic resonance imaging, computed temography, etc [2]. Among the different inorganic nanoparticles, gold is one of the fastest found metals which has become a crucial biotechnological tool. The property of gold nanoparticles (AuNPs) depend upon their shape and size and other parameters such as colour like orange, and red-brown are exhibited by spherical AuNPs, different absorption band has been shown because of different shape, size, surface ligand, core charge, etc [3]. Bigger diameter gold particles display higher scattering and shift towards longer wavelength while small particles of gold primarily absorb light and have peaks near 520 nm [4]. Size-dependent synthesis allows the surface plasmon resonance of AuNPs [5].

There are different physical and chemical methods utilized for the synthesis of AuNPs such as laser ablation, photochemical reduction, and electrothermal synthesis, but synthesized nanoparticles in those methods exhibit an unfriendly nature in biological systems. So green synthesis process is utilized by the researchers to make them more biofriendly [6].

From the physicochemical point of view, AuNPs are chemically inert, highly stable, biologically compatible, stable, and crystalline, those parameters are analyzed by using various analytical techniques such as X-ray diffraction (XRD) and X-ray photoelectron microscopy (XPS) for crystalline nature determination, Transmission electron microscopy (TEM) and Scanning electron microscopy (SEM), Atomic force microscopy (AFM) for surface morphology. UV-visible spectroscopy has been used to determine the size and concentration of gold nanoparticles [7]. The composition of AuNPs was analyzed through Nuclear magnetic resonance (NMR) and mass spectrometry for gold contain determination. Except those different Chromatography and electrophoresis are also used in the characterization of AuNPs [3, 8].

Surface-modified AuNPs are very useful for multiple applications such as diagnostic, nanotechnology, biomedicine, etc. There are so many methods available for the surface modification of AuNPs like, polymer coating, chemical reduction, physical sorption secondary modification. Among them chemical reduction is mostly used. Those process can improve stability, penetration property, solubility, surface charge, biological interaction of gold nanoparticles [9].

Synthesis of gold nanoparticles

Synthesis of gold nanoparticles involves two main components one is a reducing agent (like polyols, citric acid, and sulfites) and another one is a stabilizing agent (Sulphur and phosphorus ligand, polyvinyl pyrrolidone, chitosan) [10]. Reducing agent is the most important component involved in AuNPs synthesis from gold chloride by reducing gold ions to gold atoms. Reducing agents also can act as stabilizing agents involved in the prevention of aggregation and the size and shape of AuNPs depend on the choice of reducing agent for instance iron sulfate is used for gold nanoparticle synthesis whereas hydroquinone and ascorbic acid are preferable for gold nanorod synthesis [11]. Stabilizing agents like chitosan can control the morphology and optical properties of AuNPs along with the prevention of aggregation. A stabilizing agent like polyethylene glycol has also shown their impact in minimizing cytotoxicity and improving the biocompatibility of these nanoparticles [12]. So, both of those agents are important considerations for the synthesis of AuNPs as they can affect the size shape, stability, and biocompatibility of nanoparticles [13].

Two different approaches have been widely used in nanoparticle synthesis, the top-down approach and the bottom-up approach. Synthesis of gold nanoparticles was not exception of that. In the top-down approach, large material broke down and size was reduced towards nanoscale so this process is also known as the destructive method [14]. Bottom-up approach involves assembling of nanostructure through different intramolecular or interatomic forces (Van dar Waals, electrostatic) because of its constructing phenomena this process is also known as the constructive approach which shown in Fig. 1 [15].

Among different syntheses green synthesis of AuNPs has gotten special attention in recent times because of its cost-effectiveness, biocompatibility, and environmental sustainability [16]. Green synthesis of AuNPs involve the extraction of plant biomolecules through different extraction process like solvent-based extraction, maceration, microwave-assisted extraction, etc. plant bio-extract is mixed with the gold salt for the reduction of gold ions and formation of AuNPs that confirms from the colour change of the solution which shown in Fig. 1. A group of scientists reported green synthesis of Ca- AuNPs by using dried *Capsicum annum* extract and obtained stable nanoparticles [17]. Another research group prepared AuNPs via *Aspergillus trinidadensis* extract. These fungi extract work as reducing and capping agents and capable to formulate stable nanoparticles that are rough spherical in shape which is confirmed by SEM and TEM images [18].

In another study water extract from Hibiscus sabdariffa leaves was used as a reducing and stabilizing agent for the green synthesis of AuNPs from chlorogenic acid and the involvement of major antioxidant compounds was observed in this reduction process as compared to previous studies. Spherical shape and stability were confirmed also confirmed in this study [6].

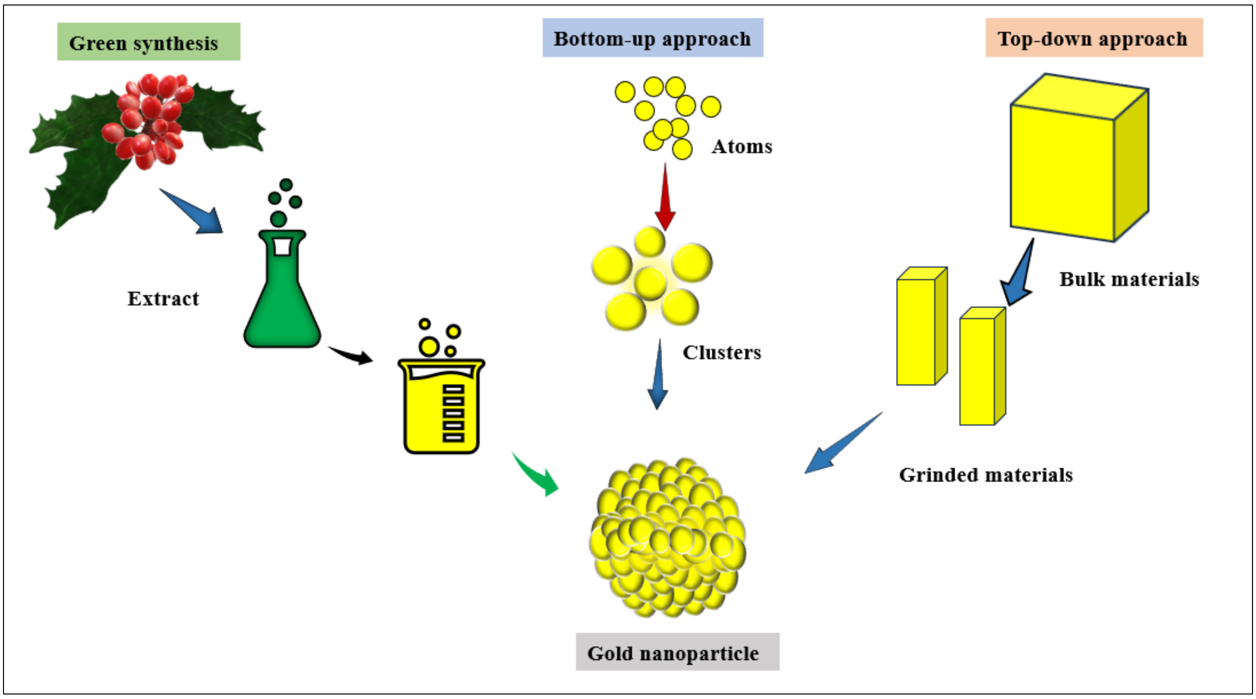

Fig 1: Different process of gold nanoparticle synthesis.

Characterization of gold nanoparticles for biomedical application

General characterization of gold nanoparticles involves the determination of shape, size, interaction, stability, crystallinity, elemental composition, surface chemistry, etc by different analytical methods. The choice of analytical methods depends on the specific application and properties has to be analyzed [19].

UV-visible spectroscopy: This process calculates the concentration of AuNPs solution by working on the principle of Beer-Lamberts law, where absorption of UV light is measured when light passes through it. AuNPs exhibit localized surface plasmon resonance because of collective oscillation of electrons in the conduction band which produces a strong absorbance band in the visible region 500 nm- 600 nm [20]. This analytical process analyzed AuNPs through the comparison between wavelength and absorbance. The optical properties, stability, quantification, and confirmation of synthesis of liquids containing gold nanoparticles are often measured by using UV-visible spectroscopy. AuNPs prepared by Patil *et al.*, (2023) through green synthesis confirm the absorption peak of AuNPs at 540 nm [17]. Another green synthesis of gold nanoparticles shows its UV absorption peak between 530-570 nm [18].

Dynamic light scattering: This is us determining the scattering of light by AuNPs due to Brownian motion. This analytical technique is used for size determination, aggregate formation, bioconjugate, and biomolecular binding studies which tell about the stability of the formulation [30]. This technique used in the determination of zeta potential, polydispersity index, particle size, and average zeta potential was suggested for stable nanoparticles ranging from -40.0 to +40.0 mV. Patil *et al*. (2023) obtained a stable formulation of gold nanoparticles in an average zeta potential of -26.0±0.8 mV which shown in Fig. 2 [17]. Other studies also confirm the stability of AuNPs in -22.9 Mv, -32.0 mV [22].

Fourier transform infrared spectroscopy (FTIR): This technique is used in the identification of functional groups in specific infra-red frequency and provides a graphical representation between % transmittance and wavenumber which is helpful from a structural elucidation point of view [23]. This process also analyzed the interaction of AuNPs with other molecules such as enzymes, amine, and phosphate groups [24]. Slight sifting of FTIR peaks can happen due to the presence of surface metals or biomolecular coating of nanoparticles, shifting of absorption peal to 3448.72 from 3525.87 was observed in Acer pentapomicum leaf extract mediated synthesis of AuNPs [25].

X-ray diffraction (XRD): This process is typically used for atomic configuration determination of the crystal structure of AuNPs. This process works on the scattering of X-ray and the diffraction is produced when scattered X-ray engage in constructive interaction which allow to differentiate between different crystalline phase [26]. Patil *et al*. (2023) obtained four different peaks in the green synthesis of gold nanoparticles at 111, 200, 220, and 300 and obtained 2ϴ values of 37.78˚, 44.02˚, 64.58˚, and 77.32˚ and comparison of that value with previous research confirm the crystalline structure of AuNPs which shown in Fig. 2 [17].

Scanning electron microscopy (SEM): This process is utilized for morphological structure and dimension determination of AuNPs. Literature review shows different structures of gold nanoparticles like, spherical, hexagonal, polygonal, triangular, etc. This widely used technique is very useful in the biomedical and industrial application of AuNPs and is also used to observe biological interaction, penetration of skin, etc. [27].

Transmission electron microscopy (TEM): This fundamental technique is used in nanoscience for high-resolution visualization of gold nanoparticles. This technique analyzed the size, and atomic structure of nanoparticles. Deshmukh *et al*. (2023) used high-resolution TEM and obtained a size of 14-33 nm, spherical shape of gold nanoparticles [18]. In another study spherical shape of green synthesized gold nanoparticles ranging from 20 – 30 nm was observed [17]. TEM image of Ca- AuNPs was shown in Fig. 2 [17].

Thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC): These analytical techniques are used to determine the purity of nanomaterial. In TGA mass of the sample was analyzed over time as the temperature changed. Both of those technique provides valuable information regarding phase transition, adsorption, desorption, thermal decomposition, etc. Thermal decomposition of *Aspergillus trinidadensis* capped gold nanoparticles shows additional thermal stability in both DSC and TGA but conventional phase transition in gold nanoparticles [18].

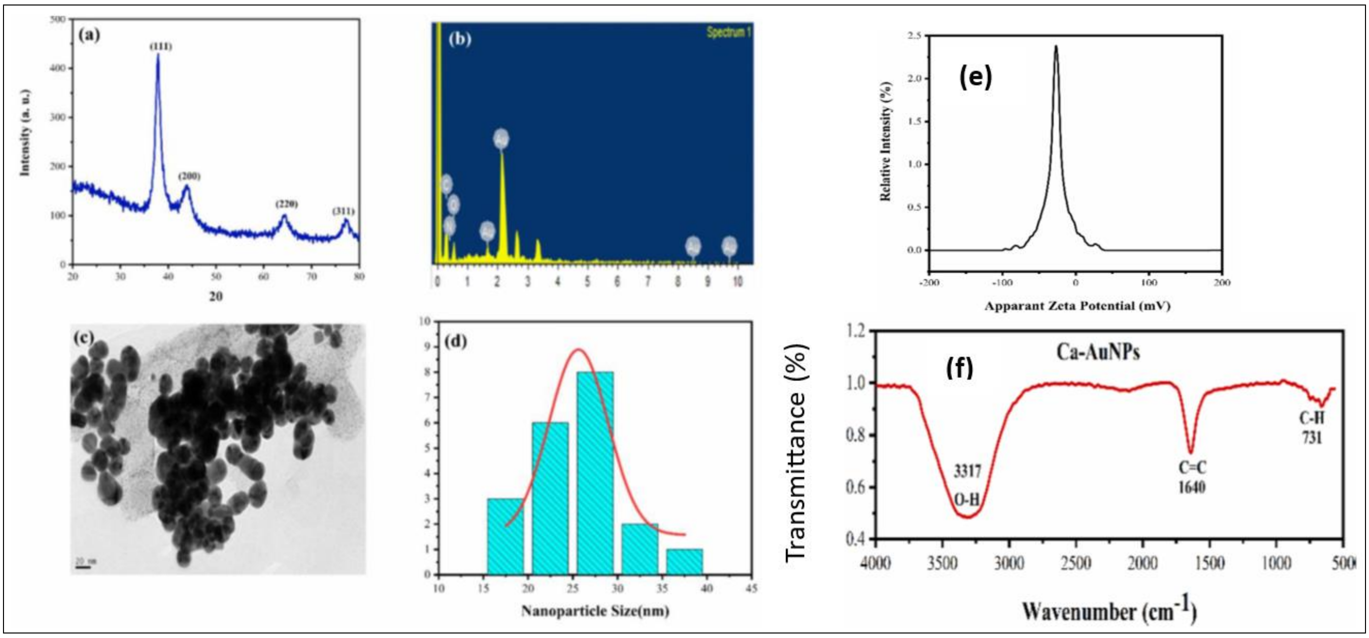

Fig 2: (a) XRD analysis of Ca- AuNPs. (b) EDAX spectrum of Ca- AuNPs. (c) TEM image of Ca- AuNPs at 20 nm scale. (d) Depending on TEM image nanoparticles size distribution histogram of Ca- AuNPs. (e) Zeta potential of biosynthesized Ca- AuNPs. (f) FT-IR spectra of Ca- AuNPs. Reprinted from Patil *et al*. [17] under open access license.

Application

Green-synthesized AuNPs are better anti-inflammatory agents than chemically synthesized AuNPs, they are capable of reducing inflammatory cytokine through the inhibition of NF-kB. Inhibition of heat-mediated inflammation was observed in *Capsicum annum* mediated synthesized AuNPs [17]. Protection from free radicals involves the activity of antioxidants. Green synthesized AuNPs display high antioxidant activity. *Capsicum annum* mediated AuNPs exhibit much better antioxidant activity than vitamin C in the DPPH assay. Those nanoparticles show their efficiency in cancer therapy and diagnosis, wound healing, tissue treatment, etc [28, 29].

Conclusion

Synthesis of gold nanoparticles by using plant extract as a reducing and stabilizing agent avoids any kind of harmful chemical and is highly efficient for biomedical applications. Physio-chemical characteristics of those nanoparticles are determined through different analytical methods, among them, a few important are discussed in this short communication. Green synthesized AuNPs show their efficiency, and biocompatibility in drug delivery, researchers also identified their potential against cancer and neurodegenerative disease.

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