

Review Article

Green Synthesis of Silver/Gold Nanoparticles, Mechanism and Applications: A systematic insight

Abstract

Green nanoparticle can be synthesized with the aid of phytochemicals in plant extracts. The phytochemicals stabilize the synthesised nanoparticles eliminating the use of toxic capping agents. Silver and gold green nanoparticles (Ag NPs, Au NPs) are common. They have wide applications in areas such as diagnosis, drug delivery and therapeutics. Despite their great applications, particle agglomeration greatly hinders their usage. As such, we explore various synthetic methods used to obtain green nanoparticles. Reaction mechanisms of the phytochemicals and precursor metals used to obtain the nanoparticles are studied in detail so as to get to the core of the problem. Use of broths obtained by boiling fresh plant leaves, stem, roots, bark or peels of fruits is the most widely used synthetic pathway. Reaction temperature, pH and metal concentration are crucial factors controlling agglomeration and particle size. Furthermore, incorporation of sunlight in the synthetic pathway was found to be economically important. The functionality of the as-synthesized nanoparticles can be modified through careful selection of the plant material used. Specifically, use of ethnomedical plants such as *Azadirachta indica* leaves, *Hibiscus rosa-sinensis*, *Ocimum tenuiflorum*, *Azadirachta indica*, *Mentha spicata*, and *Citrus sinensis* is documented to produce nanoparticles with therapeutic functions. It is desirable to obtain small size none agglomerated green nanoparticles as the size of the nanoparticles affects their antimicrobial activity. In addition, smaller nanoparticles are more effective in drug delivery.

Keywords: Green nanotechnology; Silver nanoparticles; Gold nanoparticles; Phytochemicals

1.0 Introduction

Green nanotechnology involves development of clean technologies, to minimize potential environmental and human health risks associated with the manufacture and use of nanotechnology products and to encourage replacement of existing products with new

nano-products that are environmentally friendly throughout their lifecycle (Faramarzi, M. A. & Sadighi, A. 2013; (Narayanan & El-Sayed, 2005). Green synthesis of metallic nanoparticles mostly utilizes extracts of various biological materials and plant parts (i.e. leaf, stem, seed, peel or root) as a natural source of raw chemicals to facilitate reductive synthesis of metals from a metal salt solution, consequently producing biocompatible nanoparticles using cost effective methods (Allafchian, Mirahmadi-Zare, Jalali, Hashemi, & Vahabi, 2016; Bhau et al., 2015; Elemike, Onwudiwe, Ekennia, Ehiri, & Nnaji, 2017; He, Zhang, Guo, & Gu, 2008; M. Khan et al., 2013). It is the small size of these nanomaterials as well as their large surface-area-to-volume-ratio which gives them their remarkably different properties (e.g. biological, catalytic function, mechanical properties, melting point, optical, absorption, thermal and electrical conductivity) as compared to the same material in bulk form (Guisbiers, Mejía-Rosales, & Leonard Deepak, 2012; Hartland, 2004). The phytochemicals present in the plant extracts act as stabilizers for the synthesized green nanoparticles and no additional stabilizers and capping agents are needed in most cases. The reduction mechanism is capable of controlling the size and stability of the nanostructure produced. The stability of nanoparticles can be attributed to the formation of stable bonding between metallic nanoparticles and phytochemicals present in the leaf extract (Kanchana, Devarajan, & Ayyappan, 2010). This review considers a systematic insight into green synthesis of Ag NPs and Au NPs, mechanisms of synthesis and application of the nanoparticles.

1.1 Nanoparticles

A nanoparticle is any material with its dimensions in nanometer scale or at least one of the dimensions is approximately ~100 nm (Cervellino, Giannini, Guagliardi, & Ladisa, 2005). Nanoparticles exist in different sizes, shapes, mono-dispersity and morphology.

They are different from those of the corresponding bulk materials (C. N. R. Rao & Cheetham, 2001; Suganthi, Sri Ramkumar, Pugazhendhi, Benelli, & Archunan, 2017). For instance, nanoparticles develop shapes that include spherical, triangular, cubical, pentagonal, rod-shaped, shells, ellipsoidal among others (**Figure 1**) (J. H. Park et al., 2004). Because of their distinctive optical, magnetic, and catalytic properties, they have received much attention in the fields of electronics, chemistry, biotechnology and medicine. These properties determine the applications of the nanoparticles. For example, gold nanoparticles are being used to enhance electroluminescence and quantum efficiency in organic light emitting diodes (J. H. Park et al., 2004; Wagner, Kirner, Mayer, Albert, & Köhler, 2004). Palladium and platinum nanoparticles are used as efficient catalysts (Narayanan & El-Sayed, 2005).

There are two major groups of nanoparticles; organic and inorganic. Organic nanoparticles are preferred to the inorganic nanoparticles because their synthesis processes are more friendly in terms of cost and the resulting nanoparticles are environmentally friendly. The synthesis method employed depends on the properties of the material used, type of nanoparticles to be synthesized and the expected application of the synthesized nanoparticles. The parameters that influence synthesis need to be optimized since they ultimately affect characteristics of the desired nanoparticles (Slepicka, Kasálková, Siegel, Kolská, & Švorčík, 2019). The technique used, type of polymer selected and stabilizer used influence the properties of the prepared nanoparticles (Slepicka et al., 2019). Carbon nanoparticles are also considered organic nanoparticles (Slepicka et al., 2019; Žáková et al., 2017). Inorganic nanoparticles will include magnetic nanoparticles, gold nanoparticles, silver nanoparticles and semiconductor nanoparticles (Slepicka et al., 2019).

Glucose sensors are developed from silver nanoparticles (Aslan, Jian, Lakowicz, & Geddes, 2004) and iron oxide nanoparticles are used as contrast agents in diagnosing cancer in Magnetic Resonance Imaging (MRI) (Riviere, Boudghene, Gazeau, Roger, & Pons, 2005). Gold nanoparticles have also been used as scaffolds for molecular recognition of elements and molecules (Drechsler, Erdogan, & Rotello, 2004), in optoelectronics and data storage (Lee 2010), in nanotechnology with molecular switches (van der Molen et al., 2009) and motors (Pollard et al., 2008) or in light-harvesting assemblies (Mackowski, 2010).

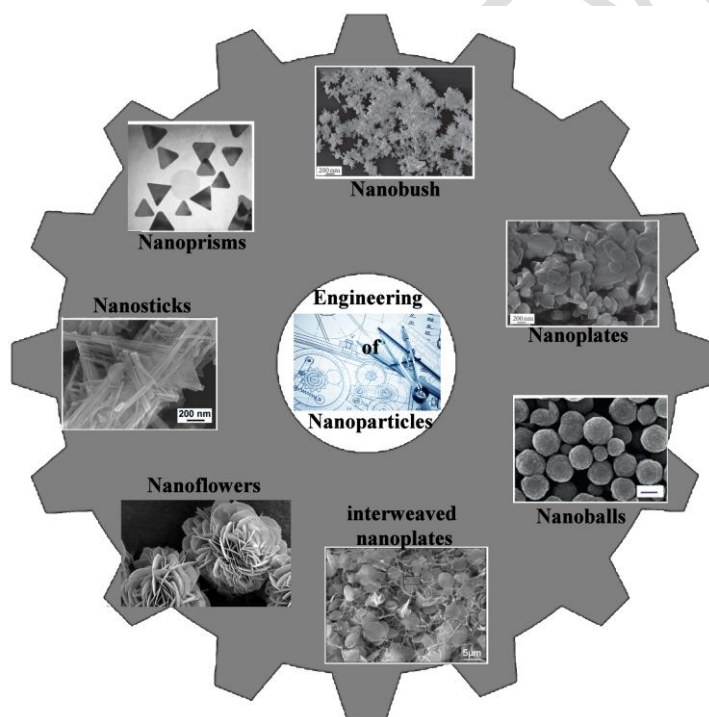


Figure 1: Engineering of different shapes of nanoparticles (Gore *et al.*, 2016; Omwoma, 2020; Omwoma *et al.*, 2020).

2.1 Synthesis of Green Nanoparticles

Various synthesis methods have been developed to formulate nanoparticles, including chemical, physical, and biological methods (Deyev et al., 2017; Khutale & Casey, 2017).

.Green synthesis of metallic nanoparticles (MNPs) by different plant parts such as the leaf, stem seed and roots has been considered to be the simplest, cost effective, reproducible, dependable, and environmentally friendly (Kalaifarasi, Jayalakshmi, & Venkatachalam, 2010; J. Kim et al., 2010; B. Kumar, Smita, Cumbal, & Debut, 2014; Verma, Kharwar, & Gange, 2009). This led to the genesis of green synthesis of nanoparticles which offers an alternative route utilizing the natural ingredients present in plant extracts. This development has helped to overcome the drawbacks of the traditional herbal drugs (Ansari et al., 2012).

Plants produce more stable metal nanoparticles and have proved to be the best candidates for fast and large-scale synthesis as compared to microorganisms (Armendariz, Herrera, & Peralta-Videa, 2004; Dutta, Paul, & Chattopadhyay, 2016; Sanghi & Verma, 2009). The preference for plants and their derivatives in nanomaterial production lies in the plants' natural composition of different organic reducing compounds, which easily adapt to the synthesis of nanoparticles (Mukunthan & Balaji, 2012). Different herbs and plant sources include higher antioxidants that are available as phytochemical constituents in seeds, fruits, leaves and stems. Therefore, the utility of plant-based phytochemicals in the overall synthesis and architecture of nanoparticles creates an important symbiosis between natural/plant sciences and nanotechnology. This association gives a characteristically green approach to nanotechnology, referred to as green nanotechnology. These production processes can be carried out without significant environmental pollution, thereby setting new standards in highly sustainable and economically viable clean and green technologies (N. Kumar et al., 2016; Matlin, Mehta, Hopf, & Krief, 2015; Shankar, Rai, Ahmad, & Sastry, 2004; Zambre et al., 2013).

In a study, biosynthesis of self-dispersed silver colloidal particles for sensing *dl*-alanine was done using edible fruit aqueous extract of *Physalis peruviana* and 1 mM Ag NO₃ with synthesis taking nearly 2 hrs at a temperature of 28 °C (Rashid & Sabir, 2014). In another study, biogenic synthesis of silver nanoparticles was done using the outer accrescent fruiting calyx of *Physalis peruviana* fruits under different light source conditions (Patra et al., 2018). Plants materials have also been utilized in synthesizing crystalline magnetite nanoparticles (Ishak, Kamarudin, & Timmiati, 2019). Biosynthesis of iron nanoparticles (Fe NPs) has been performed using extract of green tea (KSV, Reddy, & Zamare, 2017a). Crystalline monodisperse magnetite (Fe₃O₄) nanoparticles have also been synthesized by the carob leaf in a one-step reaction (Awwad & Salem, 2012). An aqueous solution of ferric chloride hexahydrate and ferrous chloride tetrahydrate molar ratio of 2:1 was mixed, and magnetite nanoparticles with an average diameter of 8 nm were obtained (Awwad & Salem, 2012). Pattanayak and Nayak (Pattanayak & Nayak, 2013) exploited the different plant resources such as mango leaves, green tea leaves, rose leaves, oregano leaves and curry leaves for production of metallic iron nanoparticles.

Green synthesis of different types of nanoparticles from plant extracts have been reported, among them are plant extracts from *Aloe Vera* leaves (Chandran, Chaudhary, Pasricha, Ahmad, & Sastry, 2006) and aqueous leaf extract of *Ananas comosus* (Olajire & Mohammed, 2021). Green synthesis of nanoparticles has also been done from extracts of the following plants; Leaf extract of *Coriandrum sativum* (M. Z. H. Khan, Tareq, Hossen, & Roki, 2018), leaves of *Bischofia javanica* (L.) (Karthik et al., 2016), *Daucus carota* extract (Luque et al., 2018), *Solanum lycopersicums* extract (Bindhu & Umadevi, 2014), *Hibiscus cannabinus* leaf extract (Suvarta et al., 2020), leaf extract of lemon grass

(KSV, Reddy, & Zamare, 2017b), leaf extract of *Bacopa monnieri* (Jawarkar, Shete, & Kane, 2019), *Citrus unshiu* peel extract (Basavegowda & Lee, 2013) and lemon grass (*Cymbopogon flexuosus*) (Kumari et al., 2016).

Much attention has been given to the high yield production of nanoparticles particularly Au NPs of defined size (0.1 -100 nm). The use of plant extracts as reducing agents can control the shape, size, and mono-dispersity of the nanoparticles (Gurunathan et al., 2009). In a study, green synthesis of Ag NPs was carried out using fresh aqueous extract of *Ixora coccinea* leaves and the spherical-shaped nanoparticles were found to have an average particle size of 13–57 nm (Karupppiah & Rajmohan, 2013) while in another study, spherically-shaped Ag NPs of small size 5–35 nm were synthesized by using aqueous leaves extract of *Ficus religiosa* plant and were effective for Dalton's ascites lymphoma (DAL) treatment in mice model (Antony et al., 2013).

The biological methods allow for more ease in the control of shape, size, and distribution of the produced nanoparticles by optimization of the synthesis methods. Different precursors which are mostly plant extracts and temperature ranging from ambient temperature to between 25 °C and 100 °C have been optimized for synthesis (Kumari et al., 2016);(Riaz et al., 2021). Other than that, pH optimization ranging from 3 to 11 have been used with the most preferred condition being alkaline (Riaz et al., 2021). Moreover, the concentration of plant extracts equally plays a role and in most cases is serially diluted from concentration of 35 mg/l. The flavonoids and phytochemical compounds of the plant extract work as reducing and stabilizing agent during the synthesis of NPs (Singh, Armstrong, & Lipsky, 2005). These include; ethylene glycol (EG) and polyvinyl alcohol (PVA) (Khanna et al., 2005). At higher concentration of gold salt, the cell free

extract concentration becomes less, resulting in insufficient capping and stabilizing action of reducing agents). In a study, two concentrations of gold salt, 250 and 500 mg/L were taken and their effect on shapes and sizes at different temperatures, 30, 40 and 50 °C were observed with 10% cell free extract. At the lower concentration, particles formed were smaller as compared to the particles formed at 500 mg/L (Kumari *et al.*, 2016).

1.2 Green synthesis of gold and silver nanoparticles

Metallic gold can be reduced to gold nanoparticles (Au NPs) by a variety of reducing agents. Green synthesis may involve the production of Au NPs using biological system such as microbes, fungi and plant extracts (Anastas & Eghbali, 2010). Synthesis of Au NPs involving plants is noteworthy due to its simplicity, rapid rate of synthesis, eco-friendliness and are potentially more biocompatible with biomolecules (Varma, 2014).

The Au NPs have many varieties of applications, which includes cancer hyperthermia treatment (Hauck, Jennings, Yatsenko, Kumaradas, & Chan, 2008; J. Lee, Chatterjee, Lee, & Krishnan, 2014), surface-enhanced Raman spectroscopy (Qian et al., 2008), and infrared radiation absorbing optics (S. Lee et al., 2008). As a result of this, a variety of synthetic procedures for the synthesis of various shapes and sizes of Au NPs have been reported (Grzelczak, Perez-Juste, Mulvaney, & Liz-Marzan, 2008).

The use of plant extracts has shown a lot of success in growing nanoparticles. Research studies have employed use of broths obtained from boiling fresh plant leaves for green synthesis (Ganeshkumar, Sathishkumar, Ponrasu, Dinesh, & Suguna, 2013; Y. Rao, Inwati, & Singh, 2017). For instance, Au NPs have been prepared using several plant extracts that include *Azadirachta indica* (Neem) leaves (Shankar et al., 2004), *Hibiscus*

rosa sinensis (D. Philip, 2010), *Ocimumtenuiflorum*, *Azadirachta indica*, *Mentha spicata* leaves, and *Citrus sinensis* (Y. Rao et al., 2017). Studies show that the antioxidants in these plant extracts are responsible for reduction of metal salts and consequently the growth and stabilization of Au NPs (Y. Rao et al., 2017). Plant extracts have a variety of compounds which include active components phenol and flavonoids, cardiac glycoside, alkaloid, saponins, tannins, steroids and terpenoids among others (Hussain, Ismail, Sadikun, & Ibrahim, 2011; Nahrstedt & Butterweck, 2010). Most of the plants have been found to contain free radical scavenging molecules such as phenolic compounds, nitrogen compounds, vitamins, reducing sugar, terpenoids and some other metabolites that are rich in antioxidant activity (Khatri & Chhetri, 2020). Moreover, all of the plants used to synthesize nanoparticles are known to be rich in polyols and antioxidant. Hydroxyl and carboxylic groups present may act as reducing agent and stabilizing agents in the synthesis of nanoparticles (Vilchis-Nestor et al., 2008). As much as the active components may be working synergistically, the combined components may equally affect their respective pharmacokinetic behavior thus hampering the plant's safety and efficacy (Qiao et al., 2012).

Synthesis of Au NPs using sunlight has been considered a great advancement over existing chemical and physical methods as solar energy is considered to be the largest source of carbon neutral renewable energy, cost-effective, eco-friendly and traceless in chemical processes (Luo & Sun, 2007). Photochemical method have the following advantages: controlled reduction of gold (III) ions can be carried out without using excess reducing agent; radiation is absorbed even in the presence of light-absorbing solutes and products: the reduction reaction is uniform in the solution and finally the rate of reaction

is well known since the number of reducing equivalents generated by radiation is well defined (Dong, Tang, Zhou, & Zhao, 2004).

The photochemical method does not require any specific instrument for synthesis making it cheap and reliable. A number of research studies have been reported on the use of sunlight for synthesis (Cheng, Yin, Lin, Wiesner, & Bernhardt, 2011; Chien, Huang, Wang, & Yeh, 2011; Luo & Sun, 2007; Shamprasad et al., 2019; Zarchi et al., 2011). It's reported that size controlled Au NPs were synthesized using citrate as a stabilizing agent under sunlight irradiation (Luo & Sun, 2007). Similarly, Pienpinijtham and his co-workers demonstrated the synthesis of Au NPs under sunlight irradiation using starch as a reducing and stabilizing agents (Pienpinijtham et al., 2012). In this synthesis, solar energy is used to reduce the gold salt (Lan et al., 2013) and hence produce anisotropic Au NPs (N. Li, Zhao, & Astruc, 2014). Synthesis at room temperature of gold nanoparticle has also been employed and has been considered very cheap, fast and reliable. The synthesis of the Au NPs was done at room temperature and sunlight mediated.

Among various metal nanoparticles, Ag NPs obtain more attention due to its good conductivity, stability and antimicrobial activity (Roy & Bharadvaja, 2017). The biological activity of Ag NPs depends on various factors such as size, shape, surface chemistry, distribution, particle composition, particle morphology, capping, agglomeration, etc. (Carlson & Schrand, 2008). Lead nanoparticles' physicochemical properties increase the bioavailability of therapeutic agents (L. Wang, Hu, & Shao, 2017). Therefore, Ag NPs with controlled structures that are uniform in morphology, size, and functionality are important for various applications (Roy & Bharadvaja, 2017).

Ag NPs are mainly used as antibacterial and antioxidant agents, and they have been successfully applied in cancer identification and therapy (Y. Sun, Zhang, Ma, Wei, & Liu, 2016). Ag NPs synthesised from chemical methods show less antibacterial activity compared to those synthesized from biological approach which is attributed to the presence of protein coating of nanoparticles obtained from plant extract (Ahamed, Khan, & Siddiqui, 2011).

In the green chemistry approach, many investigations have reported the synthesis of Ag NPs by using plant extracts. Methods such as hydrothermal, microwave-assisted, photo-irradiation and sonication have been used for synthesis of Ag NPs (Fatimah & Indriani, 2017). For example, Ag NPs have been synthesized using *Lantana camara* flower extract by reflux, microwave and ultrasound methods (Fatimah & Indriani, 2017). Some studies used plant extracts of *Bergenia ciliata*, *Zizyphusxylopyrus*, *Malus domestica*, *Clitoriaternatea* and *Solanum nigrum*, *Nictantesabror*, *Zelanicumbark*, *Sargassum angostifoliu*, *Lantana camara* and apple extracts using Reflux, Microwave and Ultrasound Methods (Fatimah & Indriani, 2017).

1.3 Mechanism of synthesis of nanoparticles

Various methods of synthesis of nanoparticles by various methods have been employed with little information provided on mechanism of synthesis (Elavazhagan & Arunachalam, 2011; Nadagouda & Varma, 2008; Sathishkumar, Krishnamurthy, & Yun, 2010). Understanding the mechanism of synthesis and biochemical pathways that result to the formation of the metal nanoparticles is necessary for understanding of the process and hence applications of the nanoparticles. Several hypotheses have been floated for synthesis of nanoparticles (Duran & Seabra, 2012; Y. Park, Hing, Weyers, Kim, & Linhardt, 2011; Rai, Yadav, & Gade, 2008; Thakkar, Mhatre, & Parikh, 2010). The

biogenic reduction of metal nanoparticles is attributable to the existence of diverse bioactive molecules that include amino acids, aldehydes, phenols, carboxylic acid, ketones, and nitrogen-bearing compounds, which are responsible for reduction and capping: for the stability of the synthesized metal nanoparticles (Kuppusamy, Yusoff, Maniam, & Govindan, 2016). One method for synthesis of nanoparticles is by photosynthesis. However, mechanism of hypothesis is yet to be given in a detailed manner (Duran *et al.*, 2011). In a research study at using geranium plant (Shankar, Ahmad, Pasricha, & Sastry, 2003a; Shankar, Ahmad, & Sastry, 2003b) it was found that the aqueous leaf extract of this plant contains proteins and secondary metabolites. The terpenoids in the leaf extract was postulated to contribute to reduction of silver ions and themselves oxidized to carbonyl groups. This was supported by FTIR analysis where a band of 1748 cm^{-1} was assigned to ester C=O group of chlorophyll (Shankar *et al.*, 2003a). Synthesis of gold nanoparticles using the same plant extract showed that proteins in the extract were responsible for capping of gold nanoparticles. Another study done at National Chemical laboratory (NCL) to synthesize pure metallic and bimetallic nanoparticles using neem leaf broth (Shankar, Rai, Ahmad, & Sastry, 2004a) reported that while reducing sugar in the broth could be responsible for the reduction of metal ions and the formation of corresponding metal nanoparticles, flavanoid and terpenoid were surface active molecules responsible for stabilizing the synthesized nanoparticles. The flavanoid and terpenoid constituents of neem leaf broth were believed to be the surface-active molecules stabilizing the nanoparticles (Shankar *et al.*, 2004a).

In another biogenic synthesis using extract of lemon grass (*Cymbopogon flexuosus*), it was reported that the reduction of AuCl_4 by reducing sugars (aldoses) lead to formation of gold nanoparticles with triangular shapes. Further, aldehydes/ketones were speculated

to influence the shape of the nanoparticles synthesized. They were also found to bind with the nascent nanoparticles rendering them “liquidlike” and amenable to sintering at room temperature (Shankar *et al.*, 2004b). Tamarind leaf broth was also used in biosynthesis of gold nanoparticles to investigate capping and stabilization of the nanoparticles using tartaric acid (Ankamwar, Chaudhary, & Satry, 2005a). In a study done by (J. L. Gardea-Torresdey *et al.*, 2002) on synthesis of gold nanoparticles inside living plants, it was not possible to provide mechanism for the synthesis until after a year when a study done on alfalfa showed that its roots are capable of absorbing silver as Ag (0) from the agar medium and then transfer it to the shoot portion in the same oxidation state (J. L. Gardea-Torresdey *et al.*, 2003). The analysis by transmission electron microscopy (TEM) showed that silver atoms accumulated inside the alfalfa plant tissues undergo nucleation and subsequently form nanoparticles. In a similar biogenic synthesis of silver and gold nanoparticles using *Cinnamomum camphora* leaf extract, (J. Huang *et al.*, 2007) it was reported that polyols were mainly responsible for the reduction of silver and/or chloraurate ions. However, while working with palladium nanoparticles using the same plant, this group reported that heterocyclic components were responsible for the reduction of palladium ions to palladium nanoparticles as well as for their stabilization (Yang *et al.*, 2010). (Nadagouda & Varma, 2008) also reported the green synthesis of silver and palladium nanoparticles using coffee and tea extracts. In their hypothesis, after the complexation with Ag and Pd metal salts, their reduction into Ag and Pd nanoparticles and capping with oxidized caffeine/polyphenols occur simultaneously.

A study on synthesis of gold nanoparticles using *Avena sativa* (oats), reduction of Au (III) to Au nanoparticles showed that functional groups such as carbonyl, amino, and sulfhydryl present in the cell wall may also contribute to the reduction (Armendariz *et al.*,

2004). In a similar study using *Chilopsis lineasis*, inductive coupled plasmon (ICP) and X-ray diffraction (XRD) spectroscopy were applied to determine the phytoextraction by gold (J. Gardea-Torresdey et al., 2005). In this study, it was postulated that the ionic form of salt was transported across the root membrane and translocated inside the plant followed by a reduction process to the metal elements. In extraction of silver nanoparticles using chilli extract, (S. Li et al., 2007), proposed a model of “recognition–reduction–limited nucleation and growth”. In his explanation of the model, in the recognition process, the silver ions are first trapped on the surface of the proteins present in the chilli extract via electrostatic interaction. Thereafter, the silver ions are reduced by these proteins leading to changes in the protein + secondary structure and the formation of silver nuclei, which can subsequently grow by further reduction of silver ions, and hence, the resulting elemental silver can accumulate on the preformed nuclei. In this way, the formation of stable spherical silver nanoparticles take place.

According to (Begum, Mondal, Basu, Laskar, & Mandal, 2009), kinetic studies using FTIR and cyclic voltammetry showed that polyphenols or flavonoids present in tea leaves were responsible for the Ag and Au nanoparticle synthesis. This group reached to this conclusion as no Ag or Au nanoparticle was observed in the leaf extract lacking polyphenols/flavonoids. (Sheny, Philip, & Mathew, 2013) employed tea polyphenol in the synthesis of Pt NPs. The phenolic compounds present in tea polyphenols served as both reducing and capping agents by forming complexes with the Pt ions, reducing them to nanoparticles of diverse sizes and morphologies (E.-Y. Kim, Ham, Shigenaga, & Han, 2008; Nadagouda & Varma, 2008; Porcel et al., 2010).

Similar results have been reported by (Sathishkumar, Sneha, & Yun, 2009) during their study on Pd nanoparticle synthesis using *Curcuma longa* tuber extract. (Raghunandan et al., 2009) found that flavonoids present in the guava leaf extract were responsible for the synthesis of gold nanoparticles. This also is supported in study by (Aromal & Philip, 2012) who reported that flavonoids in fenugreek seed extract were powerful reducing agents that may be responsible for the reduction of chloroauric acid whereas the carboxylate group present in proteins can act as a surfactant to attach onto the surface of gold nanoparticles and stabilize them through electrostatic stabilization.

A study reported that plants have limited capacities for reducing the metal ions and the capacity depends on the reduction potential of metal species (Haverkamp & Marshall, 2009). The study showed that the uptake of various silver salts solution by hydroponically grown *Barssica juncea*, they proposed that metal nanoparticle formation by plants is restricted to noble metals. In a similar study on synthesis of silver nanoparticles using latex of *Jatropha curcas*, (Bar et al., 2009) reported the involvement of cyclic octa-peptides (Curcacyclin A and B) for the reduction of Ag⁺ to Ag nanoparticle and curcain, an enzyme present in the latex of *Jatropha. curcus*, for their stabilization. However, a study by (K. B. Narayanan & N. Sakthivel, 2011) reported that plant-mediated synthesis could not occur by enzymes because generally the plant extract is heated to 90 °C during the synthesis process. According to them, phytochemicals such as phenolics, terpenoids, sesquiterpenes, and flavonoids and the functional groups present in these phytochemicals are involved in the reduction and capping of nanoparticles. Phytochemicals comprising functional groups, such as hydroxyl and methyl groups, can serve as both reducing and capping agents in the biosynthesis of metal nanoparticles (Aygun et al., 2020).

In another study, (Kasthuri, Veerapandian, & Rajendiran, 2009b) used apiin, a flavonoid glycoside isolated from heena leaves for the synthesis of anisotropic Au and quasi-spherical Ag nanoparticles. Analysis using FTIR spectroscopy, confirmed that the carbonyl group of apiin contributes to the interaction between the nanoparticles and apiin. According to (Song, Jang, & Kim, 2009) terpenoids and reducing sugars were responsible for the synthesis of metallic nanoparticles. In their synthesis of gold nanoparticles using *Magnolia kobus* it was noted that terpenoids having the functional groups of amines, alcohols, ketones, aldehydes, and carboxylic acids were responsible for the stabilization of gold nanoparticles. (Dwivedi & Gopal, 2010) predicted the possible involvement of carbonyl group and carboxylate ions present in *Chenopodium album* leaf extract and their influence on the reduction process and stability of precious metal nanoparticles, respectively. There has also been assumption that water-soluble compounds such flavonoids, terpenoids, and thiamine are capping agents for Au nanoparticles (D. Philip, 2010) while (V. Kumar, Yadav, & Yadav, 2010) concluded that the amount of polyphenols present in plant extracts were responsible for determining the size and distribution of synthesized silver nanoparticles.

There has been new development in the recent past regarding synthesis of metal nanoparticles with their possible mechanism (Aromal & Philip, 2012; Vanaja & Annadurai, 2012). (Prathna, Chandrasekaran, Raichur, & Mukherjee, 2011) in their study on synthesis of silver nanoparticles using Citrus lemon extract, demonstrated the ability of citric acid to act both as the principal reducing agent for the nanoparticle synthesis as well as stabilizing agent for the synthesized silver nanoparticles. In a similar study using callus extract of *Citrullus colocynthis*, investigations showed that polyphenols with

aromatic rings and a bound amide region were attached to the surface of the synthesized silver nanoparticles (Satyavani, Ramanathan, & Gurudeekan, 2011). Another study showed that saponins present in the aqueous leaf extract of *Memecylon edule* contributed to the reduction of silver and gold ions to form silver and gold nanoparticles respectively (Elavazhagan & Arunachalam, 2011). While researching on the synthesis of gold and silver nanoparticles, (Y. Park et al., 2011) reviewed the use of plant-derived polysaccharides and phytochemicals as the reducing and stabilizing agents in the green synthesis of gold and silver nanoparticles. It was shown that the oxidation of the polysaccharide hydroxyl group in the carbonyl group plays an important role in the reduction of metal salt into nanoparticles. In addition, the reducing end of polysaccharide can also be used to introduce an amino functionality capable of complexing and stabilizing metallic nanoparticles. For (Vanaja & Annadurai, 2012), their study on *Coleus aromaticus* leaf extract-mediated synthesis of silver nanoparticles speculated that the presence of aromatic amine, amide (I) group, phenolic groups and secondary alcohols were reducing agents responsible for the synthesis of nanoparticles. According to (Thirumurugan, Aswitha, Kiruthika, Nagarajan, & Christy, 2016), biosynthesis of Pt NPs using *Azadirachta indica* extract showed distinct FTIR peaks at 1728.22, 1365.60, and 1219.01 cm^{-1} for Pt NPs corresponding to carbonyls, alkanes, and aliphatic amines, respectively. They postulated that *Azadirachta indica* leaf broth contains terpenoid which is capable of reducing and stabilizing the nanoparticles (Song, Kwon, & Kim, 2010).

(Ganaie, Abbasi, & Abbasi, 2018) reported that the polysaccharides and proteins in the *Antigonon leptopus* plant extract were responsible for the reduction of Pt ions to Pt NPs as well as the stabilization of Pt NPs, while (Nishanthi, Malathi, & Palani, 2019) in their synthesis of Pt NPs using *Garcinia mangostana* rind extract assigned the bands around

1,430–1,440 cm^{-1} and 1,275–1,285 cm^{-1} in the FTIR spectrum of Pt NPs to the secondary aromatic amines and polyols such as hydroxyl flavones and hydroxyl of xanthenes. They concluded that the amines and polyols contained in *Garcinia mangostana* rind extract were also responsible for reduction and stabilization of Pt NPs.

Figure 2 shows a schematic diagram of synthesis and mechanism of nanoparticles

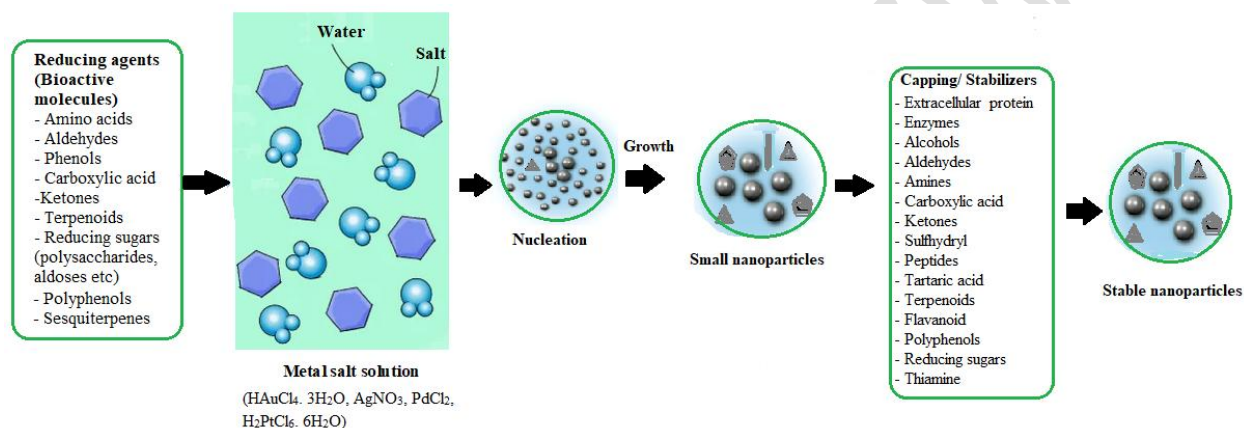


Figure 2: Schematic diagram of synthesis and mechanism of nanoparticles

2.4 Factors affecting green synthesis of nanoparticles

Green synthesis as any other chemical reactions will always be affected by a number of factors. Of prime is be the synthetic protocols and raw materials used. The main factors include concentration of the precursor and the plant extract, pH, time of synthesis and ratio of the metallic salt to the plant extract.

2.5 Effect of pH on synthesis of nanoparticles

In synthesis of nanoparticles, pH of reaction mixture is very important (Armendariz et al., 2004). Morphology of NPs produced is affected by variation in pH of reaction mixture. For instance, (Armendariz et al., 2004) reported that in oat biomass matrix, variations in

pH resulted in the formation of gold nanoparticles of different shapes, with majority having 20 nm in size. Smaller size NPs are known to have more antimicrobial activity than larger NPs (Chwalibog et al., 2010). In drug delivery, the smaller the NP, the longer it will remain in the circulatory system and therefore have a greater chance of being distributed among the target sites (Gaumet, Vargas, Gurny, & Delie, 2008).

In a study, the synthesis of silver nanoparticles was found to be significantly influenced by the impact of the pH, as well as temperature conditions (Riaz et al., 2021). It was found that at pH 5 and 25 °C, nanoparticles of different morphologies (spherical, polygonal, and capsule) and sizes were formed. It was also reported in the same study that increase in pH from 5 to 11 led to an increase in monodispersity of spherically shaped nanoparticles at temperature of 65 °C (Riaz et al., 2021). Moreover, in the same study, increase in pH from 5 to 9 during synthesis was found to decrease the size of particles from 9.9 nm to 5.6 nm. However, further increase in pH to 11 resulted to increase in size of the Ag NPs to 10.4 nm (Riaz et al., 2021).

Many biomolecules are considered as the source for the manufacturing of biological NPs. A study showed that biomolecules are unable to activate in acidic environment such as pH 2.0. In another study, Ag NPs and Au NPs from ginger root extract at various pH ranges from (4-10) had a greater absorbance measured using UV-visible when the pH is enhanced between 4 and 8 or 9 (Velmurugan et al., 2014). It was therefore evident that as basic pH increased, the absorbance also increased at 1.4 for Ag NPs and 2.0 nm for Au NPs with sizes of the nanoparticles ranging from 20-100 nm. A study showed that the Ag NPs absorbance value increases with the increasing pH, where at pH 11 there is a high absorption value, and there were 2 peaks that indicated different sizes of Ag NPs. A

higher absorption value can also indicate a higher number of nanoparticles (Roopan *et al.*, 2013). The difference in the value of λ_{max} and the number of λ_{max} can indicate differences related to the size and shape of Ag NPs (Aziz & Jassim 2018).

2.6 Effect of concentration

The amount of plant extract affects the morphology of nanoparticles. A number of research studies show that concentration of the plant extract affects largely the shape and size of developed nanoparticles and hence nanoparticles' biological activities (Bhuvaneswari, Thirugnanam, & Thirumurugan, 2019). In a study to investigate effect of precursor concentration using *Elaise Guineensis* (Oil palm), a set of six concentrations ranging from 0.51 mM to 4.055 mM were used to determine how it affects size and shape of Au NPs synthesized. Leaf extract effect of gold (III) precursor concentration (on size and shape of gold nanoparticles was evaluated by carrying out Au NPs synthesis experiments at 30 °C for 60 min (Ahmad, Muhammad, & Bhattacharjee, 2016). Effect of volume of gold (III) precursor (1.53 mM) added to the reaction medium containing a fixed volume of leaf extract was investigated by using volumes of 1 ml, 2 ml, 3 ml, 4 ml and 5 ml. Surface plasmon resonance (SPR) peak intensity increased when volume of precursor added was increased from 1ml to 3 ml. However, at precursor volume higher than 3 ml, the SPR intensity decreased from 533 nm to 546 nm possibly due to unavailability of sufficient amount of reducing biomolecules in the leaf extract (Ahmad et al., 2016). Volume of aqueous extract was kept constant at 2 ml in this study. Red shifting of SPR wavelength from and Au NP size enlargement were detected as the volume increased within mean particle diameter 27.89 ± 14.59 nm to 22.88 ± 8.21 nm. (Ahmad et al., 2016).

In another research study (Q. Sun et al., 2014), using tea solution in the synthesis of Ag NPs, it was found that volume to volume dilution affected synthesis. Volume by volume dilution of stock tea solution reported in that study were 1, 5, 10, 25, 50 and 100 % along with total carbon content of 1, 2, 5, 20 g/l. The greatest silver NPs were obtained at concentration of 5 %. Higher concentration resulted in unstabilization of the Ag NPs synthesized.

2.7 Effect of time and temperature

Other factors affecting synthesis of nanoparticles are time and temperature. A direct relationship occurs between the time and the intensity of colour of reaction. For example for the first 45 minutes of a reaction mixture, the reduction rate of metal ions may not be fast. In addition, the temperature of a reaction is very important when synthesizing nanoparticles and determines the morphology of the resulting nanoparticles. Chili *et al.* (2008) demonstrated the importance of reaction time and temperature in the formation of polymer mediated anisotropic Au NPs (Chili & Revaprasadu, 2008) while Shao *et al.* (2004) demonstrated aspartate mediated synthesis of triangular and hexagonal nanostructures under room temperature conditions (Shao, Jin, & Dong, 2004). The same reaction did not yield triangular and hexagonal structures when synthesized at a boiling temperature (Mandal, Selvakannan, Phadtare, R., & Sastry, 2002).

Aggregation of the nanoparticles is a limitation in application of the synthesised nanoparticles (Mazumder, Perwez, Noori, & Sardar, 2019). For instance, Au NPs without stabilizers are known to be unstable towards aggregation (Dutta et al., 2016). In a study, the effect of temperature on the aggregation kinetics of partially Au NPs was monitored in the range of 20–60 °C. The results showed that the rate of aggregation had increased

with temperature (Dutta et al., 2016; J. Park, Joo, Kwon, Jang, & Hyeon, 2007) reported that at higher temperature greater consumption of metal reactant and faster (put time) formation of small sized NPs was observed. A study to synthesize Ag NPs and Au NPs from *Zingiber officinale* root extract showed that as temperature increased from 20 to 50 °C, the absorbance of the reaction mixture also increased (Velmurugan et al., 2014). The results suggest that an elevated temperature accelerates the reduction process. Gold nanoparticles can equally be synthesized successfully by adopting sun light irradiation method. Green synthesis of nanoparticles (**Figure 2**) involves bottom-up approach for optimization of conditions for synthesis of metal nanoparticles.

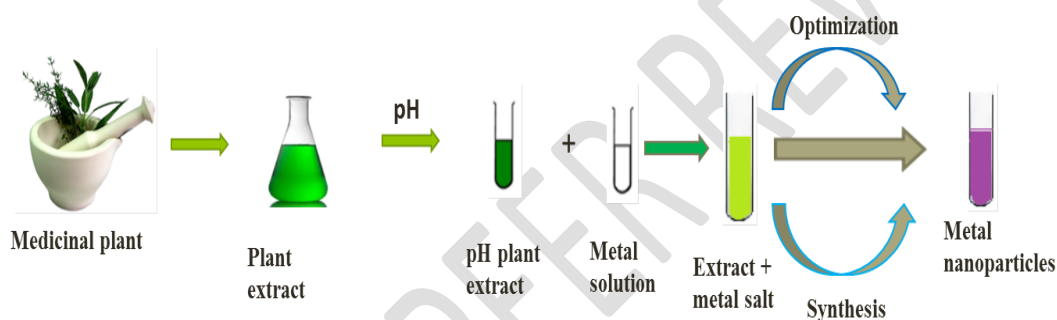


Figure 3: Green synthesis of metal nanoparticles

3 Characterization of nanoparticles

Physicochemical properties of nanoparticles are important for their behavior, bio-distribution, safety, and efficacy. Therefore, characterization of Ag NPs and Au NPs is important in order to evaluate functional aspects of synthesized particles. Characterization is performed using a variety of analytical techniques, including UV-vis spectroscopy, X-ray diffractometry, Fourier transform infrared spectroscopy, X-ray photoelectron spectroscopy, dynamic light scattering, scanning electron microscopy, transmission electron microscopy, and atomic force microscopy.

UV-visible spectroscopy is a technique for confirming types of nanoparticles synthesized by measuring Plasmon resonance and evaluating the collective oscillations of conduction band electrons in response to electromagnetic waves (Ingale & Chaudhari, 2013). It provides vital information of the synthesized nanoparticles in terms of their sizes, structure, stability and aggregation (Danieland & Astruc, 2004). Metal nanoparticles are associated with specific absorbance bands in characteristic spectra. For example, Ag NPs produce a absorbance peak between 400 and 450 nm (Agnihotri, Mukherji, & Mukherji, 2014), while Au NPs have an absorbance peak between 500 and 550 nm and this is due to the excitation mode of the surface plasmons, which vary depending on the size of the nanoparticle (Botteon et al., 2021).

Red cabbage has been used to synthesise Ag NPs using hydrothermal method and this yielded monodispersed spherical nanoparticles exhibiting antibacterial activity towards Gram-positive bacteria *staphylococcus aureus*, Gram-negative bacteria *Escherichia coli* and Gram-negative fungus *Candida albicans* (Ocsoy et al., 2017). Orange and citrus peels have been synthesised using microwave producing Ag NPs with mean size of $7-17.31 \pm 0.84$ nm and 7.36 ± 8.06 nm respectively with synthesis of citrus peel taking only 15 min (Nnemeka et al., 2016); In the synthesis of Ag NPs from *Camellia japonica* leaf, aging at room temperature the Ag NPs exhibited photocatalytic activity in the degradation of nitrobenzene under UV-vis irradiation (Karthik et al., 2017). The formation of Ag NPs synthesized using *lantana camara* flower extract using microwave-assisted and ultrasound-assisted syntheses showed peak at around 420-450 nm due to plasmon resonance and showed that longer treatment time gives higher absorbance indicating a higher concentration of Ag NPs in the solution.

Figure 4 shows UV-vis of *Lantana camara* and Ag NPs obtained by reflux from our laboratory.

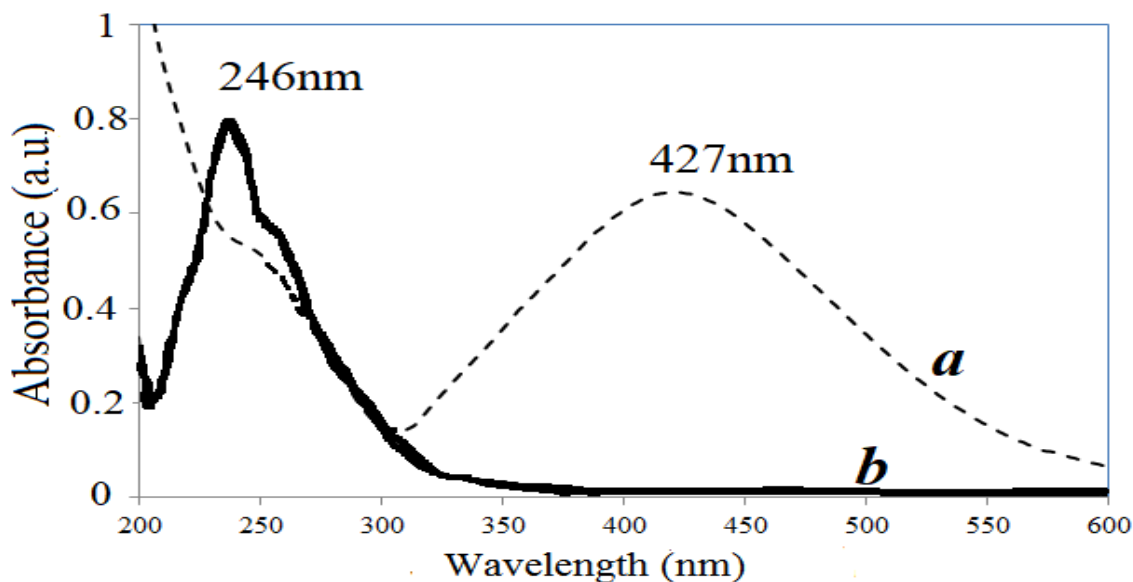


Figure 4: UV-vis spectra of *Lantana camara* and Ag NPs obtained by reflux from our laboratory (a represents *Lantana camara* extract and b represents Ag NPs) (Fatimah & Indriani, 2017).

Lantana camara extract showed a shoulder peak in the region 300-400 nm, and the maximum registered wavelength at 220 nm. The formation of Ag NPs after the reaction with AgNO_3 solution was identified from the peak at around 420-450 nm due to the plasmon resonance formation in all methods (Mohanta et al., 2017) as shown in **Figure 5**

In synthesis of Au NPs using the marine macroalgae *Sargassum muticum* the gold colloids after 15 min reaction had an SPR peak around 520 nm, which corresponded to the uniform colloids. It's worth noting that a longer reaction time produced SPR with a red shift to 550 nm causing aggregation. The pH range of 3–9, has been found to be favourable for Au NPs synthesis. However, a high protonic solution of pH 3 causes

agglomeration of the biosynthesized Au-NPs. This means the synthesised Au NPs are stable at pH range of 5-9, an aspect that is very important in synthesis of Au NPs for medical applications (Pandey & Oza, 2012).

Transmission Electron Microscopy (TEM) is one of the most commonly used methods for characterization of metal nanoparticles and specifically in determination of their shape, size, and morphology (Chauhan, Gupta, & Prakash, 2012). Using TEM, small particles (10^{-10} m in size, which is near the atomic level) can be viewed and the crystallographic structure of a sample can be imaged at an atomic scale (Pal, Jana, Manna, Mohanta, & Manavalan, 2011). **Figure 5** shows images of transmission electron microscopy (TEM) of Au NPs obtained in our laboratory.

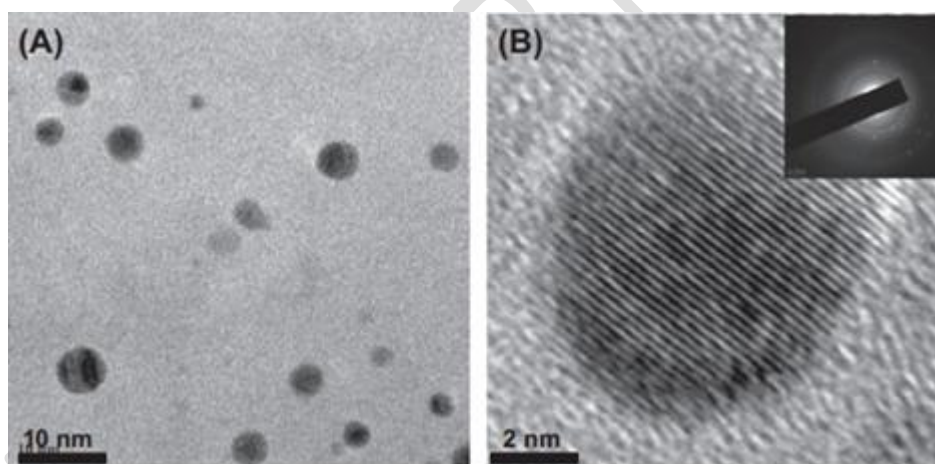


Figure 5: (A) TEM image of prepared Ag NPs and (B) high resolution TEM micrograph; inset corresponds to SAED pattern (Ahmed, Senthilnathan, Megarajan, & Anbazhagan, 2015). Figure 6 shows characterization technique.

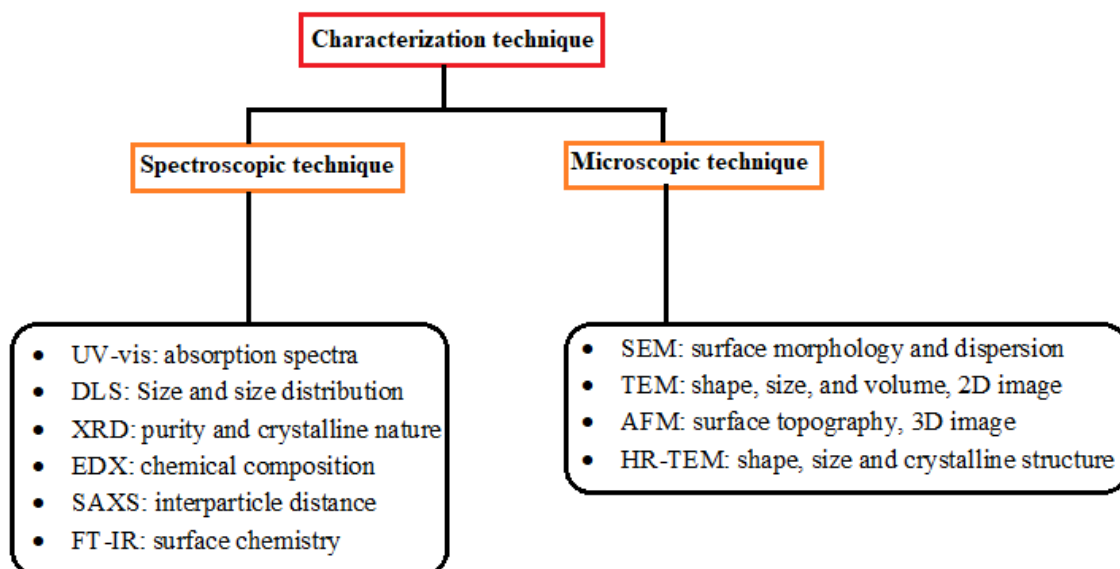


Figure 6: Characterization technique (Hu, et al., 2020)

4 Applications of green nanoparticles

4.4 Green nanoparticles as antimicrobial

The use of gold for treatment of various disorders dates back to ancient times when Chinese and Indian practitioners used powdered gold to treat many illnesses including arthritis (Parish, 1992; Raubenheimer & Schmidbaur, 2014) and its biocidal potential was first exploited by Robert Koch (Glišić & Djuran, 2014). The antimicrobial activity of Au NPs has been exploited a lot (Geethalakshmi & Sarada, 2013). The particles mostly impede the electrostatic flux across membranes which results in distorted membranes (W.-R. Li et al., 2010). Nanoparticles also enhance the expression of genes and this leads to redox processes that help in management of fungal and bacterial infection (Nagy et al., 2011). This antimicrobial potential is attributed to the distinctive surface chemistry, smaller size, polyvalent and photothermic nature of the nanoparticles (Giljohann et al., 2010).

It has been reported that interaction of inorganic nanoparticles for instance Au NPs, with microorganisms may exhibit antibacterial and antifungal activity (Chwalibog et al., 2010;

Panacek et al., 2009). The Au NPs exhibit strong cytotoxicity to varied microorganisms; the interaction with various surface-exposed functional groups present on the bacterial cell surface may lead to bacterium destruction and inactivation (Ray et al., 2007). This activity may either be as a result of coating on the Au NPs surface or to reaction contaminants left over from the manufacturing approach rather than the Au NPs cores (Ray et al., 2007).

In aerobic life of an organism, reactive oxygen species (ROS) are never welcome. These partially or activated derivatives of oxygen [singlet oxygen ($^1\text{O}_2$), superoxide anion (O_2^-), hydrogen peroxide (H_2O_2) and hydroxyl radical (HO^\bullet)] are highly reactive and toxic, possible of causing oxidative destruction of cell components (Asada & Takahashi, 1987; Wilson *et al.*, 2002). The effectiveness of ROS in damaging, as a protective or signaling factor depends on the delicate equilibrium between ROS production and scavenging at the proper site of the cell and time (Gratao *et al.*, 2005). When the rate of generation of ROS overweighs the rate at which ROS is scavenging, it leads to a harmful imbalance in the anti-oxidative system of the plant. This imbalance (often called as oxidative burst) results in widespread damage in cells including peroxidation of membrane lipids, oxidative damage to vital biomolecules such as nucleic acids and proteins and also the activation of programmed cell death (PCD) pathway probably making it possible for the NPs to initiate membrane lipid peroxidation. Consequently, the disintegration of membranes then facilitates the entrance of metals and NPs.

Figure 7 shows proposed mechanisms of action of metal NPs exposed to a bacterium (Gram-negative *E. coli*).

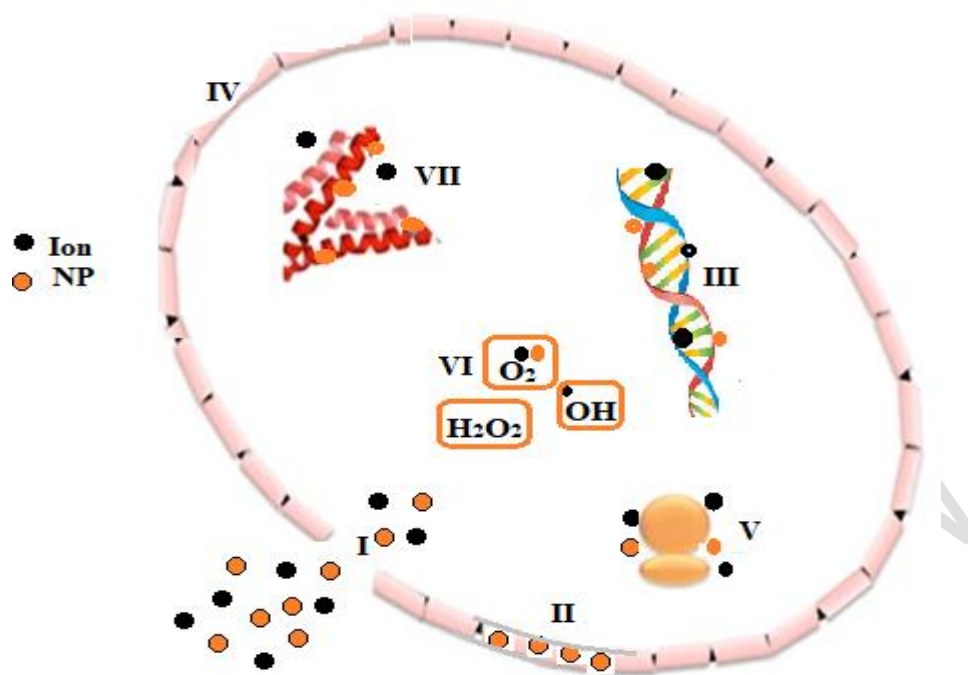


Figure 7: Proposed mechanisms of action of metal NPs exposed to a bacterium (Gram-negative *E. coli*). (I) Disintegration of cell wall allowing intracellular components to leave the cell. (II) Metal NPs entering periplasmic space, beginning a separation of the cytosol from membrane. (III) Interaction of metal NPs with DNA. Inhibition can cause ROS production. (IV) Cell pits occurring after exposure. (V) Inhibition of proper ribosome function, leading to ROS production, malformation or suppression of proteins, improper DNA function. (VI) ROS production. (VII) Interaction with proteins, specifically cysteine (Slavin *et al.*, 2017)

For medical applications, Ag NPs are by far the most popular ones (Phul *et al.*, 2016). Ag NPs are mainly used as antibacterial and antioxidant agents, and recently they have been successfully applied in cancer identification and therapy (Phul *et al.*, 2016). In another study, Ag NPs synthesized from the extracts of *Murray akoenigii* (L.) were tested for antimicrobial activity against three Gram-positive bacterial strains and four Gram-negative bacterial strains showed enhanced antimicrobial activity. Furthermore, cytotoxic

activity of Ag NPs against the HepG2 cells as well as their antibacterial and radical scavenging potential was investigated (Hanie & Taha, 2020). Cytotoxic activity was promising in a dose-dependent manner while antibacterial activity against two Gram-negative pathogen was moderate (8.14-10.22 mm) inhibition zones with promising radical scavenging potential. This shows the potential of the Ag NPs in wound dressing and other biomedical applications (S. Li et al., 2013; W.-R. Li et al., 2010; Patra et al., 2018).

There are many benefits associated with nano-formulation of herbal drugs, which include improving component solubility, enhancement of bioavailability, increasing absorbency of the organism, reducing medicinal herb doses, and achieving steady-state therapeutic levels of drugs over an extended period compared with traditional herbal drug preparations (S. Huang & Walter, 2011). Ag NPs and Au NPs have also been investigated previously for their use in targeted drug and gene delivery (Ghosh, Han, De, Kim, & Rotello, 2008; Pissuwan, Niidome, & Cortie, 2011) cancer treatments/therapy, and imaging technologies photothermal therapy of tumours (Ghosh et al., 2008; Male, Lachance, Hrapovic, Sunahara, & Luong, 2008; Sperling, Rivera Gil, Zhang, Zanella, & Parak, 2008). Moreover, Au NP based technology has been used in biosensors to detect genetic material of bacterial origin (Pissuwan, Cortie, Valenuela, & Cortie, 2010).

In environmental management, Ag NPs have been used in water treatment and purification. This may be due to its enhanced antimicrobial nature in contaminated water (Rus, Leordean, & Berce, 2017). Au-NPs with benign reactants on the other hand is also used to remove potential contamination of the colloidal solutions (Homberger & Simon,

2010) and in catalytic removal of environmental pollutants (K.B. Narayanan & N. Sakthivel, 2011).

4.5 Use of green nanoparticles in wound healing

Wound management is a challenge to mankind with two specific types of wounds; chronic and acute wounds (Harding, Morris, & Patel, 2002). Both types of wounds lower the self-esteem of the patient. Chronic wounds are considered silently epidemic and possess serious threat towards public health and global economy (WiseGuyReports, 2017). They do not heal within a predictable period of time, leading to further complications due to infections and difficulty in healing (Singh et al., 2005). Examples of such wounds include diabetic ulcers, vascular ulcers and pressure ulcers. For the case of acute wounds, they are caused by incisions and are with patients who pass through surgical treatments, traumas, abrasions or epithelial burns (Robson, Steed, & Franz, 2001). The patients are more susceptible to bacterial infections and will need new strategies (Muhammad et al., 2018).

Wound therapy has moved from drying out the wound bed to maintaining a balanced moist environment (P. G. Bowler, 2002). Traditional dressings involve absorbing wound exudate and this made the wound to develop a crust on its surface with remarkable scarring. This has since been replaced by modern dressings which aim at improving healing by handling wound fluid in a way that prevents accumulation of excess exudate while maintaining a certain degree of moisture, and thereby enhancing the chance of obtaining new skin tissue without scarring (Cutting, 2010).

Wounds are susceptible to infection due to breakage of cutaneous barrier that protects the underlying tissue against pathogens such as bacteria and fungi (P. G. Bowler, Duerden, & Armstrong, 2001). The extent of infection depends on the degree of pathogenicity of the invading organisms and the ability of the host to defend itself (Singh et al., 2005). Wound infections are mainly caused by microorganisms such as *S. aureus*, *P. aeruginosa*, *E. coli*, and *streptococci* either in their free-floating state or in biofilms where they are attached to a surface and protected by surrounding extracellular matrix produced by them. Wound dressings containing plant extract with antimicrobial compounds can be applied in order to control wound infections and significantly accelerate healing (Thakur, Jain, Pathak, & Sandhu, 2010). As wound infections can be caused by both planktonic bacteria, biofilms and fungus therefore it is essential to determine whether the plant extract loaded wound dressing has an effect on these species or not (Fonder, Lazarus, Cowan, Aronson-Cook, & Kohli, 2008).

Nanotechnology has improved treatment and diagnosis of various diseases and thus improving healthcare management (S. K. Nethi et al., 2015). Various nanomaterials have been explored for controlling microbial infections and accelerating wound healing (Ghobril & Grinstaff, 2015; Hamdan et al., 2017). Nanotechnology has impacted various fields of biomedical engineering, such as tissue engineering, regenerative medicine, gene/protein/drug delivery, and bioimaging, owing to the unique physicochemical and biological properties of nano-scale materials (Gaharwar, Peppas, & Khademhosseini, 2014; S. K. Nethi, Barui, Mukherjee, & Patra, 2019). Nanotechnology as well as nano-based approaches has become a potential platform for wound healing applications, evidenced by the numerous publications in this area (Hamdan et al., 2017; Parani, Lokhande, Singh, & Gaharwar, 2016; Zavan, Bassetto, & Vindigni, 2012). Several

polymeric, lipid-based, ceramic, inorganic, metal, and metal oxide nanomaterials have been widely investigated for cutaneous wound healing (Kalashnikova, Das, & Seal, 2015).

Au NPs are chemically stable, have the capacity of absorbing the infrared light and at the same time easy to synthesize making the particles very important in wound therapy (Niska, Zielinska, Radomski, & Inkielewicz-Stepniak, 2018). According to a research study by (Arafa & El-Kased, 2018), the surface plasmon resonance is tuned to make the Au NP gels gain thermo-responsiveness, and this improves the NPs antibacterial and healing properties, both *in vitro* and *in vivo*, a fact backed by histopathologic examinations. Au NPs can either directly target the bacterial cell wall, or they can bind to bacterial DNA, blocking the double-helix from uncoiling during replication or transcription, thus exerting bactericidal and bacteriostatic properties (L. Wang et al., 2017). As a result, they can inhibit multidrug-resistant pathogens, such as *Staphylococcus aureus* and *Pseudomonas aeruginosa* (L. Wang et al., 2017). Moreover, Au NPs prevent the formation of reactive oxygen species, thus acting as antioxidants, aiding the healing process (Vijayakumar, Samal, Mohanty, & Nayak, 2018).

It has been observed that bioactive glass induces local cell response and the release of basic fibroblast growth factor (bFGF) and vascular endothelium growth factor (VEGF). This formed the basis for a research study by (Marza & Magyari, 2019) who investigated the effect on wound healing of bFGF combined with Au NPs in Vaseline mixtures at 6, 12 and 18 wt % for 14 days. The results showed that the compound stimulated angiogenesis and fibroblast proliferation, promoting rapid wound closure, especially in the 18 wt% composite group, without causing cell toxicity. A study on *ex vivo*

permeation, showed that Au NPs can also be used in the therapy of burns, being able to promote healing and inhibit microbial colonization, while being trans-dermally active (Arafa & El-Kased, 2018).

Mechanistically, wound repair in its initial process relies on the accumulation of granulation tissue. Fibroblasts together with new capillaries proliferate rapidly and synthesize collagen fibers and matrix components. Studies have shown that nanomaterials can promote the formation of granulation tissue and promote the proliferation of fibroblasts (Nethi *et al.*, 2019; Wang *et al.*, 2021).

After the granulation tissue fills in the wound defect, keratinocytes proliferate to form an integrated epidermis. In vivo studies have confirmed that nanomaterials can promote the viability and proliferation of keratinocytes and accelerate the epithelialization of wounds. They can upregulate the expression of repair-related genes, to promote the epithelialization process. Further, nanomaterials can stimulate the secretion of various growth factors and promote the proliferation and migration of fibroblasts (Bhattacharya *et al.*, 2019).

There is usually a local collapse appearing after wound closure during the repair of some deep wounds. This collapse is probably caused by the dysplasia of subcutaneous adipose tissue during the healing process. A research study explored the influences of nanomaterials on adipose-derived stem cells (ADSCs), which have multidirectional differentiation potential to differentiate into fat, cartilage and bone (Wang *et al.*, 2021). Nanomaterials can promote the hypermethylation of the gene promoter, promotes the proliferation of ADSCs and reduces cell apoptosis at the same time promotes the adipogenic differentiation of ADSCs (Lin *et al.*, 2018).

A study has shown that nanomaterials such as nanofibers and hydrogels have hydrophilic surfaces which exhibit a high-water retention capacity and provide a moist environment for wound healing (Fu et al 2014). Ag NPs, gold nanoparticles (Au NPs), copper nanoparticles (CuNPs) and other nanomaterials can reduce the expression of matrix metalloproteinases MMP-1, MMP-3, and MMP-8 and inhibit their decomposition of collagen (Frankova et al., 2016; Lee *et al.*, 2015). These nanomaterials accelerate the remodeling of the extracellular matrix (ECM) by promoting the deposition of type I and III collagen and fibronectin, providing a beneficial environment for cell proliferation and wound repair (Wang *et al.*, 2021).

5.0 Toxicity of nanoparticles

Toxicity of nanoparticles is a concern especially the toxicity of Au NPs in drug delivery systems. A number of cell/animal models have been carried out (Alkilany & Murphy, 2010; Khlebtsov & Dykman, 2011). The general conclusion from these studies was that the Au NPs are biologically inert and almost had no toxicity (Khlebtsov & Dykman, 2011). However, this is not true when the size of gold core decreases below 2 nm, where the surface of the Au NPs showed unusual and high chemical reactivity (Alkilany & Murphy, 2010). The high surface reactivity of this size can also be the source of unwanted reactions/side effects in biological systems (Turner et al., 2008). This therefore means that there are two main divergent opinions about the toxicity of nanoparticles in literature. Some report that Au NPs are nontoxic regardless of their size or capping agents such as citrate, cysteine, biotin and sugars (Alkilany & Murphy, 2010; Connor, Mwamuka, Gole, Murphy, & Wyatt, 2005) while others report the toxicity of 2 nm cationic Au NPs as dose-dependent (Alkilany & Murphy, 2010). However, the same nanoparticles with a negative surface charge were deemed nontoxic at the same

concentrations (Goodman, McCusker, Yilmaz, & Rotello, 2004); (Alkilany & Murphy, 2010).

In a research study, several Au NPs (4, 12, and 18 nm) with different capping agents were investigated for any cytotoxicity against leukemia cells line using MTT assay (Connor et al., 2005). Results of the study showed that spherical Au NPs enter the cell and are non-toxic to cellular function (Connor et al., 2005). Another research showed that the cytotoxicity associated with gold NPs depends on dose, side chain (cationic) and the stabilizer used (Boisselier & Astruc, 2009). Cytotoxicity of gold NPs are dependent on the type of toxicity assay, cell line, and physical/chemical properties (Bahadar, 2016). Furthermore, variation in toxicity with respect to different cell lines has been observed in human lung and liver cancer cell line (Patra et al., 2018). In another research study, it was reported that while low concentrations of Au NPs enhance keratinocyte growth and differentiation, higher levels were associated with cytotoxicity (Lu et al., 2010).

Conclusion

Based on the forgoing, it's worth noting that there is no reference temperature or pH for green synthesis of nanoparticles. However, the temperature ranges from 25 °C to 100 °C with 30 °C to 80 °C being more viable and environmentally friendly. The frequent pH range utilized for synthesis equally varies from 3 to 11. However, basic pH seems to give better surface plasmon resonance based on the UV-vis spectroscopy. The UV-Vis spectroscopy complements the colours of the expected nanoparticles and helps in the optimization of parameters for synthesis on nanoparticles such as gold and silver nanoparticles. In order to produce better nanoparticles, the concentration of the plant to the gold salt would vary considering the fact that the number of phytochemicals vary

from plant to plant. Luckily it has been documented how several factors influence the quality and quantity of the synthesized nanoparticles and their characterization and ultimately applications. One should watch the following factors for desired AU and AG Nps preparations, the method used for synthesis, pH, temperature, pressure, time, particle size, pore size, environment and proximity. The stability of the synthesised nanoparticles is equally important which are controlled by compounds from the plant materials. Nanoparticles applications cover many disciplines but are recently popular for disease treatment, wound management as well as in environment management.

Data Availability

All the necessary information required for replication of this work and/or conducting secondary analysis are included within the article.

NOTE:

The study highlights the efficacy of "herbal" which is an ancient tradition, used in some parts of India. This ancient concept should be carefully evaluated in the light of modern medical science and can be utilized partially if found suitable.

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