Green Biosynthesis of Nanoparticles for Targeted Drug Delivery

Tanuja1, Isha Gaurav2

ABSTRACT

The matter at its molecular or atomic level is engineered and manufactured through a technique called Nanotechnology. It has contributed in various fields of science, including material science, biology, chemistry, and engineering. Various research studies have suggested that crude extract of plant can enhance the activity of green synthesized nanoparticles (NPs), like gold (Au) and silver (Ag). However, one drawback of NPs is its toxicity. The altered size, shape or surface chemistry of NPs help in passive or active drug targeting. If the size, shape or surface chemistry of NPs is altered, drug targeting can be helped passively or actively. Changing the size, shape or surface chemistry of NPs can help drug targeting actively or passively. On the other hand, green synthesis is said to be environment friendly in which extract of plant is used as capping as well as a reducing agent. So, green synthesis of NPs is important when studying different pathogens. In recent years, nanotechnology has been applied in treating health-related problems, which showed promising results, mainly in the treatment of cancer. The present review discusses the historical and the latest development, drawbacks, and the challenges faced in the field of green biosynthesis of NPs, along with its wide application.

Keywords: Gold nanoparticles, Green biosynthesis, Nanoparticles, Silver nanoparticles.

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INTRODUCTION

Use of advance technology for synthesizing nanoparticles plays a major role in the biomedical and human health care fields for producing a wide range of products (Pal et al., 2011). Nanotechnology means material at the atomic level can be manipulated through biological, chemical and physical approaches (Cauerhff and Castro, 2013). During the 19th century, nanoparticles of gold and silver were used by artist of Mesopotamia to create a gleaming effect on pots and utensils (Faraday, 1987). This is said to be the concept of the modern property of nanoparticle, scientifically provided through Michael Faraday in his paper “Experimental relation of Gold and other metal to Light” (Faraday, 1987; Singh et al., 2011). Richard Feynman in 1959 gave the term Nanotechnology, which was the marked initiation in the Nanotechnological world (Singh et al., 2011). By using green nanotechnology and the biotechnological tool, an environment friendly technique is evolved to produce non-toxic products all over the world (Joerger et al., 2000; Chauhan et al., 2012). As the biological method or green method used for synthesizing nanoparticle have varied nature, are stable and have accurate dimension therefore their synthesis is a one-step process. Synthesis can be processed at physiological condition like temperature, pressure, pH, at a negligible cost (Ingle and Chaudhari, 2013). So the nanoparticles for their potential applications are characterized through various characterization techniques, for that it can be used in drug delivery as well as in the biomedical field. For the synthesis of nanoparticles, clean biological root is needed (Lekshi et al., 2012). This includes various approaches like reduction in solution, photochemical and chemical reaction in aggregated molecules for thermal decomposition of nanoparticle compound (Awwad and Salem, 2012) microwave assisted process, radiation assisted, electrochemical and lately green chemistry root (Ravindra et al., 2012). For the synthesis of environment friendly as well as Pharmaceuticals and biomedical field materials such as plant extract (root, stem, bark, leaf, flower), fungi, bacteria and enzymes are being used because they do not produce toxic chemicals during synthesis (Gokulakrishnan et al., 2012). Nanoparticles have huge applications in the field of genomics, immune response enhancement, biosensor, clinical chemistry, and also perform targeted drug delivery (Diva et al., 2012).

Green Nanotechnology

The methods of synthesis of a nanoparticle are physical, chemical, biological and hybrid technology (Fig. 1) (Mohanpuria et al., 2008; Tiwari et al., 2008; Luechingere et al., 2010). Toxic end products are produced by conventional physical and chemical approaches which are hazardous to the environment. The nanoparticles used by these approaches are not used for medical purposes as it may create health issues, exclusively in the clinical field (Parashar U.K. et al., 2009; Parashar V. et al., 2009). The use of conventional method for nanoparticle synthesis at a large scale with its mentioned size and shape in less time is done but they are complicated, of high cost, ineffective and the most important they are outdated. In the recent years, huge interest has been developed in environment friendly synthesis of nanoparticle which do not produce toxic product during its manufacturing...
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**Factors Affecting the Synthesis of Nanoparticles**

Synthesis, characterization and application of nanoparticles are affected by many factors. There is a change in nature of synthesized nanoparticle when they come in contact with different adsorbates as well as catalysts used. This report was given by different researchers working on this field (Ajayan, 2004; Somorjai and Park, 2008). Few of the researchers have reported effectual nature of nanoparticle synthesized which shows varied symptoms and inferences by changing environment and time as well (Pennycook et al., 2012). A large number of factors affect the nanoparticle synthesis like pH of solution, temperature, extract concentration to be used, raw material concentration, size (Baker et al., 2013).

Some dominant factors that affect nanoparticle biosynthesis are described below:

a. **Particular method or technique:** Various protocols are implemented for the synthesis of nanoparticle which ranges from physical technique that includes mechanical procedure up to the chemical and biological approaches by the help of organic, inorganic chemical and living organisms too. These techniques used have both benefits as well as drawbacks. Among all, the biological method use of nontoxic and environmental friendly material are conjugated in green technology for synthesizing nanoparticle, so they are said to be favourable for the environment and widely accepted more than traditional methods (Kharissova et al., 2013; Vadlapudi and Kaladhar, 2014).

b. **pH:** In the synthesis of nanoparticles in green technology, pH plays an important role. It has significant effects on morphology, surface area and size of NPs. This was reported by a number of researchers (Gardea-Torresdey et al., 1999; Armendariz et al., 2004). Control over the size of nanoparticle can be done by adjustment of pH in solution medium.

c. **Temperature:** The other important parameter which influences the synthesis of nanoparticle is temperature among all three methods. The requirement of the temperature in physical method should be higher than 350°C and in chemical method the requirement is below 350°C. In many of the cases nanoparticle synthesized through green technique needs the temperature below 100°C or the nature of nanoparticle built (Rai et al., 2006).

d. **Pressure:** For the nanoparticle synthesis pressure to play an important role. When on the reaction medium pressure is applied shows effects on size and shape of nanoparticle synthesized (Abhilash, 2012). The biological material rate of reducing metal ion is much faster when ambient pressure is provided (Tran et al., 2013).

e. **Time:** The duration of time also influences the nanoparticle synthesis by using green technique. When the reaction medium is incubated according to the length of time, the quality and the type of synthesized nanoparticle are greatly influenced (Darroud et al., 2011). Likely the character of

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**Fig. 1:** Different approach and method for synthesizing nanoparticle

**Fig. 2:** Biological synthesis of nanoparticle

(Daniel and Astruc, 2004; Li et al., 2011; Chauhan et al., 2012). This can be gained by a gentle synthesis which takes place through biological nature like using a biotechnological tool which is said to be safe and environmentally sound for fabrication of nanomaterial that is the best substitute for conventional physical and chemical method (Joerger et al., 2000). This gave rise to the concept of green nanobiotechnology or green technology.

Meaning of the green nanotechnology is to synthesise nanoparticle or nanomaterial through biological routes like microorganisms, plants, and their byproducts such as protein and lipid by using different biotechnological techniques. Use of a green technique is much better than the synthesis done through physical and chemical methods. For example, green technology eliminates various expensive chemical, and less energy is utilized and produces environment friendly by-products. To produce less harmful chemical by-products and products, the researchers, scientists, chemical technologists and chemists all over the world use the twelve principles of green chemistry as a research guide (Anastas and Warner, 1998; Kharissova et al., 2013). Nanobiotechnology is used as an alternative path for synthesizing biocompatible stable nanoparticle (Narayanan and Sakthivel, 2011). As we know two different processes are used for the reduction and stabilization of NPs. The first process is the bottom-up approach and the second is the top-down approach. The bottom-up approach is applied in the synthesis through biobased in which the synthesis takes place by the help of reducing and stabilizing agent (Fig. 2). There are three steps to be followed for synthesising nanoparticles by the use of biobased product. They are 1) Solvent used for synthesis should be chosen. According to many researchers, water is considered the best suited solvent for the synthesizing process. Sheldon stated that water is the best solvent among all other solvents used (Shanker et al., 2016), 2) The reducing agent chosen for NPs synthesis should be environment friendly and 3) Nontoxic material should be chosen as capping agent so that the synthesized particle can become stable (Mohanpuria et al., 2008; Singh et al., 2011).
nanoparticles change according to the time and is affected by the process of synthesis, light exposure and storage condition (Kuchibhatla et al., 2012; Mudunkotuwa et al., 2012), if synthesized NPs are stored for longer period they may shrink or grow. They have their shelf life and therefore their potentiality is affected.

f. Preparation cost: Cost plays an important role in synthesis of nanoparticle which should be controlled and regulated to assist the potential application of nanoparticle in modern days. Therefore, effectiveness of cost in the process of producing nanoparticle is an important factor. Thus, the synthesis of nanoparticle with physical and chemical approaches is more cost effective, so the biological method used for synthesis of nanoparticle is less cost effective and is done on a large scale.

g. Particle shape and size: The properties of nanoparticle are determined by particle size. For example, when the size of a nanoparticle reaches the nanometre scale, their melting point decreases. There are many reports on this (Akbari et al., 2011). The energy of different configuration nanoparticle is similar, that helps in transforming their shape easily (Yacaman et al., 2001). The energy type used to analyze nanoparticle enhances the change in shape of a particular nanoparticle. Therefore, the effective nature and shape of particle synthesized influence their chemical property (Baer et al., 2013).

h. Pore size: The size of the pore affects the quality and application of nanoparticles. Pore size and surface modification of biomolecule has provided efficient drug delivery of various molecule (Ruckenstein and Kong, 1999).

i. Environment: The nature of nanoparticles is determined by the environment of the surrounding. Through oxidation and reduction process in much of the environment, a single nanoparticle turns out to be core−shell nanoparticle. Soon after absorbing material or showing reaction with other material (Sarathy et al., 2008). Nanoparticle synthesized by the biological approach forms a coating which is thick and large-sized (Lynch et al., 2007). On the other hand, the environment also affects the physical and chemical nature of the nanoparticle synthesized. Some examples show the effects of the environment on synthesized nanoparticle nature. When crystalline zinc sulphide nanoparticle was placed from wet to dry condition their nature changed due to the change in environment. Due to changes in environmental condition, chemical nature of Cerium nitrate NPs may vary (Kuchibhatla et al., 2012).

j. Proximity: The properties of most of the nanoparticle alter when a single or isolated nanoparticle are contacted with other nanoparticles (Baer et al., 2008). This behavioural change in such nanoparticle can give rise to turns of nanoparticles. The proximity effect of nanoparticles like particle charging, substrate interaction and magnetic property shows a great implication.

k. Other factors: Plants are rich source of secondary metabolite which plays a role in reduction and stabilization of synthesized nanoparticle. Though their composition differs in different part of plants, the type of plant and the most important is the process used for extract preparation (Park et al., 2011). Synthesized nanoparticles are also affected by the various intracellular and extracellular enzymes produced by different microorganism (Haverkamp et al., 2007). For the purification of synthesized nanoparticle, the chosen method influences quality as well as quantity of nanoparticle. On the basis of gravitational force, a centrifugation process is used to separate the nanoparticle The chromatography technique is also applied for separation of nanoparticles on the basis of mobile and stationary phase coefficient (Jimenez et al., 2003). The nanoparticle separation is important in the field of pharmaceutical and biomedical industry (Kowalczyk et al., 2011).

### Why Nanoparticles are Metal

Nanoparticles show an antimicrobial activity and it also helps in developing various diagnostic tool (Ravindra et al., 2012). Some of the nanoparticle are said to be attractive probe of biological marker due to its small size that is 1 to 100nm. Their strong affinity to the targeted protein enhancer delay their aggregation. It depends on the type of surface modification, photoemission, electrical and heat conductivity, surface catalytic activity in improved manner (Sahayaraj and Sathiyamoorthy, 2011). There are various type of nanoparticle formed by different metals, like gold, silver, copper etc, which are described below.

### Green Biosynthesis of Gold NPs

From the last few decades nanoparticles synthesized by using various metals have shown increasing importance because of their exclusive physical and chemical property and therefore are said to be the most researched topic from past few decades (Sahoo and Parveen, 2007; Safari and Zarnegar, 2014). Because of the great interest in nanoparticle synthesis researchers had a considerable focus on physical and chemical methods which include chemical reduction, hydrothermal, sol-gel, reverse micelle, ion sputtering, etc. (Kumar et al., 2013; Ahmed et al., 2015a) but these two methods are expensive and not environment friendly as they produce toxic components. Therefore, the different approaches other than physical and chemical methods applied were called the biological approach in which naturally occurring reagent like plant extract, bacteria, fungi etc can be used as reducing as well as stabilizing agent for synthesis (Krishnaswami et al., 2014; Ahmed et al., 2015a,b). Synthesis of nanoparticle through gold has attracted more because of their application in different fields such as antimicrobial, catalytic, electronic, in the biomedical field etc.

### Green Biosynthesis of Silver NPs

The demand for Silver nanoparticles has increased in various fields such as medical, food, consumer, healthcare, for industrial purposes because of their peculiar physical and chemical properties (Mukherjee et al., 2001; Li et al., 2010; Gurunathan et al., 2015). As they have a unique property so they have various applications which include antibacterial agent, healthcare related products, medical device coating, in pharmaceutical and food industry, in drug delivery, applied as an anticancer agent and the most effective anticancer drugs to kill the tumors (Chernousova and Eppe, 2013). Nano size of a silver particle can change their physical, chemical and biological properties
because of their surface to the volume ratio, so they are used for various purposes (Li et al., 2001; Sharma et al., 2009). Considering all physical, chemical and biological methods for synthesizing silver nanoparticle, the best is the biological approach as it does not produce any toxicity.

**Green Biosynthesis of Copper NPs**

Nanoparticles synthesized through Copper are used in different fields like industrial engineering, technological field, agriculture etc. For the synthesis of Copper nanoparticles, biotechnology has used different biological, physical and chemical approach to produce nano size particles with exclusive function. Copper nanoparticles have antibacterial properties which have increased their demand in the field of agriculture research. This leads to the establishment of clean, cost-effective as well as systematic biosynthetic technology (Shobha et al., 2014). Nanoparticles synthesized by using copper have attracted the researcher more in comparison to silver and gold, as they are available at low cost (Han et al., 2006). Because of the catalytic, electrical, antifungal, antibacterial applications, copper nanoparticles have achieved significant importance in the field of nanotechnology as well as nanomedicine (Ponce and Klabunde, 2005; Huang et al., 2008). Various processes for synthesizing copper nanoparticles are used. One of the processes is thermal reproduction (Joeger et al., 2000), polyol method (Park et al., 2007) etc. But in recent few years, syntheses mediated by plant have acquired much more interest because of their simple and ecofriendly approach.

**Green Biosynthesis of ZnO NPs**

Nanoparticles produced through metal oxide have wide range as they are applicable in various fields like electronic, photonic devices (Engelbert et al., 2011; Zbigniew et al., 2017) and the biomedical field (Ramos et al., 2017). Advancement in the field of green synthesis brought zinc oxide nanoparticles application in the nanomedicine field. Much research has concluded that Zinc nanoparticles have the antimicrobial property (Justin and Thomas, 2012).

**Green Biosynthesis of Iron NPs**

Recently much research has reported the potentiality of iron nanoparticles in terms of environment remediation. Materials at nano scale such as nano adsorbents, nano catalyst, nano filtration, nano biocides are used for remediation as well as tackling water pollution. Among other metals, iron nanoparticles are more advantageous to overcome environmental pollution. Because of the large surface area to the volume ratio, iron nanoparticles in the field of environmental remediation showed a great interest (Lin et al., 2008; Gui et al., 2012).

**Green Biosynthesis of Titanium Dioxide NPs**

In the world of nanotechnology research, synthesis of nanoparticles is done. Recently, Titanium dioxide is being used to synthesize nanoparticles which is applied in various fields due to their optical property, high chemical stability, and most importantly, they do not produce any toxicity (Hoffmann et al., 1995; Fujishima et al., 2000). Recently much interest is shown by the researchers as it resists microbes against various metal ions, antibiotic and also developed resistant strain (Gong et al., 2007). It also shows antibacterial property (Allahverdiyev et al., 2011).

**Green Biosynthesis of Gold-Silver Alloy NPs**

Metallic alloys like Au-Ag alloy have the peculiar property in them. They have various applications in photonics, pharmaceutical industry, biological tagging, etc. (Wang et al., 2006; Som and Karmakar, 2009; Doria et al., 2010). Their activities depend on their size, composition and shape (Link et al., 1999) for different purposes. Au-Ag alloy is used like as cell biomarker and also used in measurement of drug taken by cancer cell (Balogh et al., 2006). Various methods like physical and chemical are used for the synthesis of Au-Ag nanoparticles. Recently, it has been reported that synthesis of metal alloy can be done by using biomass of fungus and mushroom (Senapati et al., 2005; Sawle et al., 2008; Philip, 2009).

**Green Biosynthesis of Cadmium Sulfide NPs**

Various sources are used for preparing cadmium sulphide nanoparticle like cadmium nitrate, cadmium acetate, cadmium chloride, cadmium oxalate as well as cadmium sulphate. Among the different semiconducting materials, cadmium sulphide used for the synthesis of nanoparticles is given more importance because of their use in drug delivery system or as a carrier in drug delivery to the desire site (Goud et al., 2016). Various challenges are faced by different researchers working in the field of nanotechnology for developing clean, environment field, nontoxic protocol (Prasad, 2017). Therefore, the green synthesis approach like using plant extracts, microbes, metabolites like a capping agent gives ecofriendly and nontoxic effect other than different approaches (Kang, 2008; Reddy, 2016).

**Why is green synthesis**

Synthesis through green approaches shows advancement over physical and chemical methods due to cost-effective, ecofriendly, simply scaling up for large scale synthesis of nanoparticle. In green synthesis, high pressure, energy, temperature and toxic chemicals are not needed.

**The Green Route for Biosynthesis of Nanoparticle**

For synthesizing nano and micro length scaled inorganic material that has contributed for developing new and unexplored field of research on basis of biosynthesis of nanoparticle, nontoxic and safe reagent is used (Salam et al., 2012). Among all the green processes for synthesizing nanoparticle plants are supposed to be easy and simple process for producing nanoparticle at large scale. They are collectively called as biogenic nanoparticles (Fig. 3).

**Biological Method**

Preparation of extract through bio-organism behaves as reducing and capping agent in synthesis of nanoparticle. The bio organism extracts for synthesizing nanoparticle have different bio-molecules like protein/ enzyme, polysaccharide, amino acid and vitamin which help in reducing metal ion by combining with them. They are said to be environment friendly though they are chemically complex. Much research has reported on the synthesis of nanoparticle through various compounds present in bio organism (Sahayara and Rajesh, 2011) because of its ecofriendly nature and simplicity. The biological synthesis of nanoparticles created a marked importance.
NANOPARTICLE DRUG DELIVERY SYSTEM

As we know that the nanoparticles have potential ability to reduce toxic compound of therapeutic agents in their surrounding cells and also increase the number of drug in targeted cell so they have become centre for attraction in drug delivery (Tolaymat et al., 2010). The nanoparticles that are characterized are further coated with drugs and established into the body. After reaching the specific site, they function accordingly. The significance of targeted drug delivery is that they move the drug specifically to the sites of infection which are treated without any harm to the body (CD Creative Diagnostics, 2018). The small volume of nano carrier depicts the physical, chemical and biological characteristics which make them advantageous to be used as medicine. Nanoparticle with its physical, chemical and biological characteristic are used up by the cell in the easy manner than the larger molecule; therefore, they are stoultly applied as equipment for delivery in recently used biological active cells. The drug is combined by cell specific object to mostly composed particle. In the drug delivery system, many of the small particles are involved like dendrimers, liposomes, silicon, carbon material and magnetic nano carrier. As we know that peculiar properties of nanoparticles are related to their small size that is 1-100 nm and their large surface to its volume ratio, the drug delivery system supplies required dose with less side effects and toxic production. Overall, nanoparticles solve the problem which is related to drug solubility and bioavailability. The nano carrier helps in protecting the drug from harmful environment. Their origin may be organic or inorganic that can be prepared from various polymer ceramic, metals etc. Among all metals, silver is more profitable preferable than others. It has antibacterial, antifungal, antioxidant and physiochemical properties in comparison to the bulk materials like optical, electrical, thermal and catalytic property (Tolaymat et al., 2010; Le Ouay and Stellacci, 2015; Phull et al., 2016). In spite of various therapeutic agents, silver nanoparticles are alternative strategy for drug delivery system to cure cancer as they directly or indirectly targeting tissue of tumour. It was seen that if drug is accumulated at its required side, it enhances the effectiveness of anticancer therapy. Different silver nanoparticles synthesized through the green approach have anticancer activity that offers the opportunity for new treatment.

CHALLENGES IN GREEN CHEMISTRY

In the recent years, we have seen immense advancement and growth in the field of nanotechnology. The new development and discoveries are considered centre for attraction in medical treatments as they are powerful, less toxic curative that they can enter into the area of disease and behave as magic bullets. Different researchers in pharmaceutical industries have developed some nanomedicine that are being successfully developed as well as accepted for clinical use. But still nanomedicine fields are at their early stage with little success stories; therefore, the review has explored huge challenges that experienced while developing nano based therapeutic.

Firstly, it is important to know the reason for the development of nanomedicine. Nanoparticle shows there peculiar property at the atomic, cellular and molecular levels but not visible in bulk material (Emerich and Thanos, 2006) due to their high surface to volume ratio. Nanoparticles are able to produce three dimensional structures which is pliable to design drug delivery system that is further used as they may fulfil many required properties like potentiality to overcome biological barrier, ability to deliver hydrophobic water soluble molecule and also have potentiality to select the target site in the body.

BIOLOGICAL BARRIER IN DRUG DELIVERY

There are numerous biological barriers for drug which create hindrance for them in reaching to their deliberated site. The delivery of the drug blood-brain barrier (BBB) creates hurdles in the delivery of drugs (Xiaowei, 2018). In circulation, drugs need to overcome a few barrier for reaching the target. The blood brain barrier (BBB) limits the spreading of hydrophobic molecule in Cerebro-spinal fluid and is a great hurdle for treating many of the CNS as well as brain disorder Many nanoparticles are planned for delivering drug over blood brain barrier (BBB) which include liposome, nanosphere and cation albumin nanoparticle. Delivery of hydrophobic compound shows consequential obstacles in pharma industry as formulating hydrophobic drugs needs toxic solvent and surfactants like Cremophore and Tween, which impair distribution of drug and shows several harmful effects. Therefore, newly synthesized nanoparticles-based medicines require to successfully overcome various hindrance before it is approved to go in market. So, nanostructure development is to be done with suitable component and their properties. Nanotechnology is being widely used for commercial production all over the world. But still there is little information in concern of increasing human, animal and environment expose to nanoparticles specially silver nanoparticles, as well as the risk related to short and long term toxicity

CONCLUSION

With this we come to the conclusion that nanotechnology is said to be the science that deals with production, approaches and the most important manipulation of particles. Because of their advanced characteristics, they are applicable in many fields like farming, nanofertilizers, petroleum, clothing etc. Green synthesis
of nanoparticle is said to be ecofriendly in nature therefore it is important when different pathogens are studied. It is applied for the treatment of various health related problems. Various methods are applied for nanoparticle synthesis that is physical, chemical and biological with the help of plant, microorganism and many other sources. Characterization of the nanoparticles is done by the manipulation of their size and shape. It was observed by many of the researchers that certain changes in shape and size of medicine and their properties is done through activated nanoparticle. A small drug with large activity targets the specific site. In recent days nanoparticles have become popular transport system of medicine. So, synthesis of nanoparticles may serve in the field of biomedical industries in developing various drugs for the ailment related to living beings. Though nanoparticles based drug is seeking great attention because of its therapeutic behaviour, certain challenges have been encountered during the development of nanoparticles, which have to be tackled in near future.

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