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Review article

SYNTHESIS OF SILVER NANO PARTICLES FROM PLANT EXTRACT AND ITS APPLICATION IN CANCER TREATMENT: A REVIEW

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ABSTRACT: Development of reliable and eco-friendly process for synthesis of nanoparticles is an important step in the field the of nanotechnology. Nanotechnology involves the tailoring of materials at the atomic level to attain unique properties, which can be suitably manipulated for the desired applications. Among them silver nanoparticles draw attention due to its unique physical, chemical and biological properties. Green principle route of synthesizing have emerged as alternative to overcome the limitation of conventional methods among which plant and microorganisms are majorly exploited. Employing plants towards synthesis of nanoparticles are emerging as advantageous compared to microbes with the presence of broad variability of bio molecules in plants can act as capping and reducing agents and thus increases the rate of reduction and stabilization of nanoparticles. This review focuses on the green synthesis of silver nanoparticles using various plant sources and its applications in cancer treatment. Generally surgery, chemotherapy and radiation treatment are the most prevalent therapeutic option for cancer . Unfortunately these treatments have various side effects due to lack of targeted delivery and cancer specificity. To overcome these limitations, nanoparticle could ensure targeted drug therapy having very little side effects. In this review focus is given to silver nanoparticle, synthesized from natural plant extracts, as it is cost effective, eco-friendly, stable and safe in cancer treatment.

INTRODUCTION

Nanotechnology deals with the understanding and regulating matter at a dimension of roughly 1 to 100 nanometers. It includes the understanding of the fundamental physics, chemistry, biology and technology of nanometer scale objects. It also includes how such objects can be used in the areas of computation, sensors, nanostructure materials, biomedical, agricultural, biolabeling, cancer, biotechnology and in other areas [1]. Various conventional methods have been employed for the synthesis of nanoparticles. Before adopting these methods for application in therapeutic purpose, it is important to evaluate if those methods are safe, ecofriendly, economic and not time consuming. There are two methods employed for the nanoparticle synthesis such as "Top down" and "Bottom up" process. Generally in the "Top down" process bulk materials are broken down into small particles at the nanoscale with various techniques like grinding, milling that means the nanoparticles are produced by size reduction from a starting material [2].In "Bottom up" process the nanoparticles are built by joining atoms, molecules and smaller particles [3] as shown in figure 1.

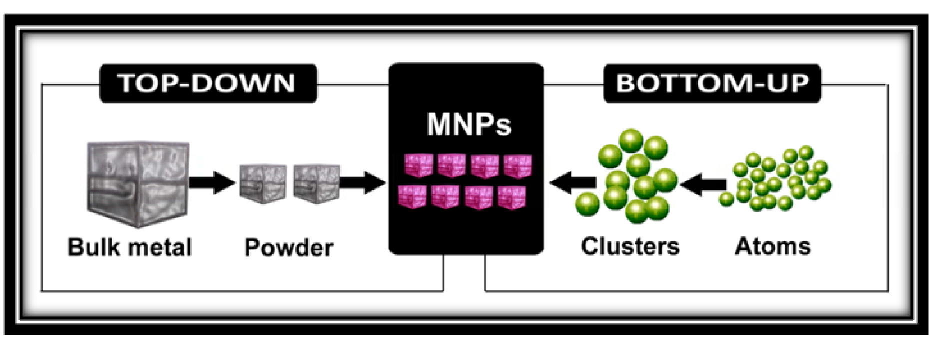

Figure 1: General methodology of synthesis of nanoparticles

There are 3 methods for preparation of nanoparticles. 1)Physical, 2) chemical and 3) biological. Traditionally nanoparticles were produced only by physical and chemical methods. Some of the common methods are ion sputtering, solvothermal synthesis, reduction and sol gel technique. The need for biosynthesis of nanoparticles rose as the physical and chemical processes were cost effective. Nature has devised various processes for the synthesis of nano- and micro-length scaled inorganic materials which have contributed to the development of relatively new and largely unexplored area of research based on the biosynthesis of nanomaterials [4] . Hence, for the biosynthesis of nanoparticles plant and microbial sources were used.

Various different methods come under physical and chemical processes like high energy ball milling, melt mixing, physical vapour deposition, laser ablation, sputter diposition, colloidal route, sol-gel method etc. Among all some methods which are commonly used in physical and chemical processes are a) Sol-gel technique, which is a wet chemical technique, where 2 types of materials or components, sol and gel are used. This method is used for the fabrication of metal oxides from a chemical solution which act as a precursor for integrated network (gel) of discrete particles or polymers. The precursor sol can either be deposited on the substrate to form a film, cast in to a suitable container with desired shape or used to synthesize powders. b) Solvothermal synthesis is a versatile low temperature route in which polar solvents under pressure and at temperatures above their boiling points are used. Under solvothermal conditions, the solubility of reactants increases significantly, enabling reaction to take place at lower temperature. c) Chemical reduction, which is the reduction of an ionic salts in an appropriate medium in the presence of surfactant using reducing agents. Some of the commonly used reducing agents are sodium borohydride, hydrazine hydrate and sodium citrate. d) Laser ablation, is the processes of removing material from a solid surface by irradiating with a laser beam. At low laser flux, the material is heated by absorbed laser energy and evaporates or sublimates. At higher flux, the material is converted to plasma. By depending upon material's optical properties and the laser wave length the laser energy is absorbed and the amount of material is removed. By this method carbon nanotubes are formed. e) Inert gas condensation, where different metals are evaporated in separate crucibles inside an ultra high vacuum chamber filled with helium or argon gas at typical pressure of few hundred pascals. As a result of inter atomic collisions with gas atoms in chamber, the evaporated metal atoms lose their kinetic energy and condense in the form of small crystals which accumulate on liquid nitrogen filled cold finger like gold nanoparticles are synthesized from gold wires.

Biosynthesis of nanoparticles

The physical and chemical processes for synthesis of nanoparticles are very costly. To overcome this limitation, researchers have found the cheapest way that is the use of microorganisms and plant extracts for nanoparticle synthesis process. The use of microorganisms in biological method have been widely established and it is a kind of bottom up approach where oxidation/reduction reaction is the main reaction[5][6][7][8][9][10][4][11][12]. Three types of green synthesis- :a) use of microorganisms like fungi, yeasts (eukaryotes) or bacteria, actinomycetes (prokryotes), b) Use of plant extracts or enzymes c) Use of templates like DNA, membranes, viruses and diatoms.

Bio-reductant from bacteria, fungi, or plant parts + Metal ions

(Maybe enzyme/ phytochemical)

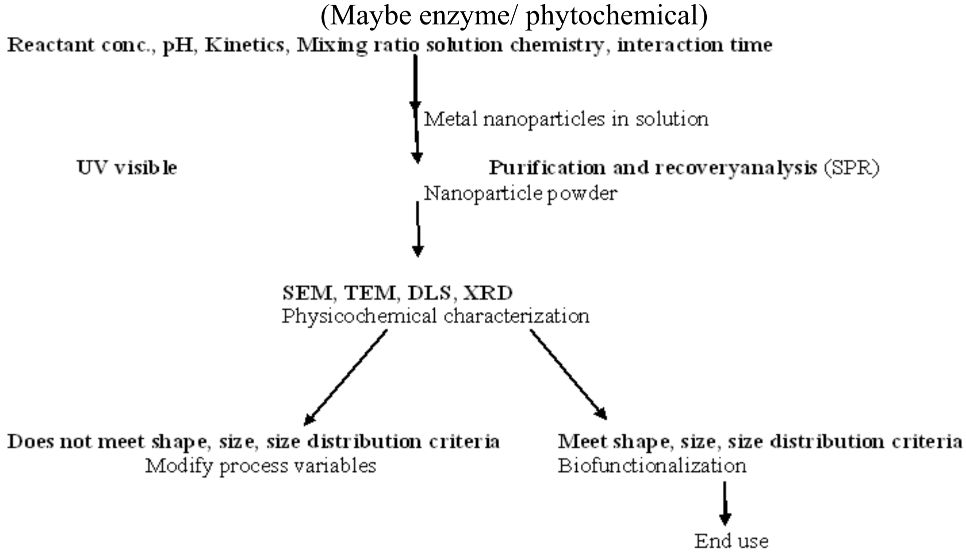

Figure 2: General methodology of nanoparticle synthesis

Synthesis using bio-organisms is compatible with the green chemistry principles because these are ecofriendly and in this process reducing agents and capping agent can be utilized [13]. As compared to chemical synthesized nanoparticles with biosynthesized nanoparticles it is found that biosynthesized nanoparticles are ecofriendly and biocompatible in medical applications.

Initially bacteria are being employed for the nanoparticle synthesis but later other organisms like yeast, fungi, actinomycetes etc are used. Microorganisms are capable of interacting with metals coming in contact with them and form nanoparticles. The cell-metal interactions are quite complex. Certain microorganisms are capable of separating of metal ions. *Pseudomonas stuzeri* Ag259 is a one type of bacteria which is commonly found in silver mines have the capacity to accumulate silver outside or inside of their cell walls. They can produce numerous type of silver nanoparticles of different shapes having size <200 nm. *Lactobacillus* strain present in butter milk, can convert low concentrations of metal ions (Au^+, Ag^+ etc) to metal nanoparticles. Some well known examples of bacteria synthesizing inorganic materials include magnetotactic bacteria (synthesizing magnetic nanoparticles) and S layer bacteria which produce gypsum and calcium carbonate layers[14]. By using fungi (*Fusarum oxysporum*), extremophilic actinomycete *Thermomonospora* sp. gold and silver nanoparticles are produced extracellulary. Also by different microbial routes semiconductor nanoparticles like CdS, ZnS, PbS etc can be produced. The production of nanoparticle using microbes is a time consuming process.

On the other hand, plant extract could be utilized as a source of nanoparticles as they are safe to handle and having a broad variability of metabolites which are required for reduction..When the use of whole plant extracts and plant tissues are evaluated, it is found that the use of plant extracts are simpler, readily scalable and may be less expensive for preparation of nanoparticles [15]. Plants are known to contain various therapeutic compounds which are being used since ancient time as a traditional medicine. Recently, various reports (Table-1) mentioned about the use of plant extracts for the production of nanoparticles, as they have advantages like these are easily available, safe and contain a broad range of biomolecules (such as alkaloids, terpenoids, phenols, flavonoids, tannins, quinines etc.), which can mediate the nanoparticle synthesis. Plant secondary metabolites have proved to be an excellent source of new medicinal compounds. There are four major classifications of plant derived anticancerous compounds such as Vinca alkaloids, Epipodophyllotoxin lignans, Taxane diterpenoids and Camptothecin quinoline alkaloid derivatives.

Since fungi and bacteria require a comparatively longer incubation time for the reduction of metal ions, water soluble phytochemicals do it in a much lesser time. Therefore compared to bacteria and fungi, plants are better candidates for the synthesis of nanoparticles.

Characterization of nanoparticles

Nanoparticles can be characterized by their shape, size, surface area and dispersity [40]. For their characterization some common techniques are used like UV-visible spectrophotometer, dynamic light scattering (DLS), scanning electron microscopy (SEM), transmission electron microscopy (TEM), Fourier transforms infrared spectroscopy (FTIR), X-ray diffraction (XRD) & energy dispersive spectroscopy (EDS) [41] [42] [43], auger electron spectroscopy (AES), X-ray photoelectron spectroscopy (XPS), time of flight secondary ion mass spectrometry (TOF-SIMS), low energy ion scattering (LEIS), scanning tunneling microscopy (STM) and atomic force microscopy (AFM), scanning probe electron microscopy (SPM) etc. UV-Vis spectrophotometer allows identification, characterization and analysis of metalic nanoparticles. Generally 300-800nm light wavelength is used for the characterization of size range 2 to 100nm [41]. The dynamic light scattering (DLS) is used to characterize the surface charge & the size distribution of nanoparticles [40]. Electron microscopy is a common method for surface and morphological characterization. Scanning electron microscopy (SEM) & transmission electron microscopy (TEM) are used for the morphological characterization at the nanometer to micrometer scale [44]. SEM can provide morphological information on the submicron scale & elemental information at the micron scale, but TEM has a 1000 fold higher resolution compared with the SEM. Characterization of nanoparticle using FTIR is very useful for the surface chemistry because the organic functional groups can be determined which are attached to the surface of nanoparticles [45]. XRD is used to examine the overall oxidation state of the particles as a function of time, i.e. phase identification & characterization of the crystal structure of the nanoparticles [46] To know the elemental composition of metal nanoparticles EDS is used [47]. AES & XPS, TOF-SIMS, scanning probe microscopy (SPM) techniques are important for the primary surface analysis of nanoparticles.

AES and XPS are used to determine the presence, composition & thickness of coating on nanoparticles, surface enrichment and depletion at particle surfaces. Sometimes XPS is used to determine particle sizes when conditions are not appropriate for analysis by other methods. TOF-SIMS is useful for obtaining molecular information about surface layers, functional groups which are added to the surface. In LEIS process the amount of energy lost by the ion during this scattering process due to a low energy ion beam can be determined. This scattering process is used to determine the identity of the elements present in the outermost surface of the material under analysis. Recently it is found that it is useful due to its high sensitivity to the outermost atomic layers of a sample [48]. AFM and STM provide surface characterization at the atomic scale.

Table 1: List of plants used for nanoparticle synthesis.

Plants	Types of nanoparticles	Size and shape	References
Acalypha indica	Ag	20-30 nm, spherical	[16]
Allium sativum	Ag	4-22nm, spherical	[17]
Aloe vera	Au, Ag	50-350nm, spherical & tringular	[18]
Azadirachta indica	Ag/Au	7.5-65nm, sperrical, tringular & quasispherical	[19]
Boswellia ovalifoliolata	Ag	30-40nm	[20]
Carica papaya	Ag	25-50nm	[21]
Catharanthus roseus	Ag	48-67nm	[22]
Cinnamomum camphora	Ag,Au	55-80nm, quasispherical	[23]
Curcuma longa	Ag	-	[24]
Datura metel	Ag	16-40nm, quasilinear superstructures	[25]
Dioscorea bulbifera	Ag	8-20nm	[26]
Eclipta prostrate	Ag	35-60nm,tringles, pentagons, hexagons	[27]
Euphorbiaceae latex	Cu/Ag	18nm Ag &10.5nm Cu	[28] [29]
Geranium leaf	Au	16-40nm	[30]
Jatropha curcas L.	Pb	10-12.5nm	[31]
Mentha piperita	Ag, Au	5-150nm; spherical	[32] [33]
Musa paradisiacal	Ag	20nm	[34]
Nelumbo nucifera	Ag	25-80nm;spherical, tringular	[35]
Parthenium leaf	Au	50nm; face centered cubic	[33]
Rosa rugosa	Ag, Au	30-60nm Ag; 50-250nm Au	[36]
Sesuvium portulacastrum	Ag	29-92nm; spherical	[37]
Tanacetum vulgare(Transy fruit)	Ag, Au	16nm Ag; 11nm Au	[36]
Vitex negundo	Au	10-30nm; face centered cubic	[38]
Zingiber officinale	Au	10nm	[39]

Nanoparticles for cancer therapy

Cancer is one of the most common problems and serious health issue in this world. It has been observed that more than one in three people will develop some form of cancer in their entire lifetime. Based on the origin, there are variety of cancer exist, such as thyroid, prostate, bladder cancer, kidney cancer, pancreatic, breast cancer, melanoma, leukemia with all types, oral cancer, colon-rectal combined cancer, etc. In cancer, cells divide and grow uncontrollably, forming malignant tumors and invading nearby parts of the body. Till date a complete cure for this prevalent disease is yet to be discovered. But since last three decades researchers and clinicians have developed various methods to either prevent or inhibit the growth of cancer. The common types of cancer treatment are surgery, chemotherapy, radiation therapy, immunotherapy and photodynamic therapy. Surgery is generally used to treat and diagnose the localized cancer in case of many neoplasm, particularly when the cancer has not metastasizes to lymph nodes or other part of the body. Radiation therapy uses high energy radiation to kill cancer cells by damaging their DNA. Radiation therapy can be provided after the surgery alone or in combination with other treatment regimens (chemotherapy). Though radiation therapy is considered as a widely accepted mode of cancer treatment but it could sensitized both cancer and normal cell death. Chemotherapy is the use of anti-tumor drugs to treat cancer by interfering the growth ability of cancer cells. Different chemotherapeutic drugs can be used in a prescribed dose in different type of cancer, which targets particular proliferation pathways. Immunotherapy is treatment that uses the host own immune system to help fight cancer. Photodynamic therapy is a treatment that uses special drugs, called photosensitizing agents, along with light to kill cancer cells. Based on the chemical structure and mechanism by which they act, the chemotherapy drugs can be divided into 4 groups: 1) Alkalyting agents which damage DNA to prevent the growth of cancer cells, 2) Anti metabolites which interfere with the replication of DNA or transcription of RNA by substituting the normal building blocks of RNA and DNA and hens forth can cause regular cell cycle arrest. 3) Anti-tumor antibiotics which include anthracyclines, actinomycin-D 4) Mitotic inhibitors which are mostly plant alkaloid derived from natural products which stop the mitosis and henceforth inhibits the growth of cell cycle. As chemotherapy could reach all the body part including cancer cells, there may be possibility of occurrence of side effects during treatment.

Table 2: Application of plant extract used in different cell lines

S. No	Plant name	Source of extract for synthesis of silver nanoparticle (SNP)	Cancer cell lines (Human)	Size of silver nanoparticle(Ag) nm	Ic50 µg/ml	Reference
1	*Citrullus colosynthis*	Fruits, leaves, Seeds, roots	HCT-116, MCF-7,Hep-G2, Caco-2	Fruits-19.267 ,seeds-16.578 ,leaves-13.376 ,roots-7.398	(Fruits) Hep-G2 =17.2 & MCF-7= 22.4 (leaves) Hep-G2=10.2, (roots) HCT-116=21.2 & Hep-G2=22.4	[55]
2	*Origanum vulgare*	leaves	A549	63-85	100	[56]
3	*Sesbania grandiflora*	leaves	MCF-7	22	20	[57]
4	*Cissus quadrangularis*	stem	Hep-2	20-56	64	[58]
5	seaweed *Ulva lactuca*	Whole micro-algea	Hep-2,MCF-7, HT-29	5-30	Hep-G2=12.5, MCF-7=37 & HT-29=49	[59]
6	*Brassica oleracea*	Cauliflower florets	MCF-7	48	190.501	[60]
7	Seaweed *Gelidiella sp.*	Whole seaweed	Hep-2	31.25	40-50	[61]

To avoid this recently, scientists have discovered nanoparticles which can be used as targeted drug delivery for cancer therapy where only the cancer cells will destroy without affecting healthy normal cells. It is also used to reduce the side effects as well as to achieve high localized concentration. Due to their huge applications in the biomedical area, these are being used as carriers for hydrophobic drugs, diagnostic and therapeutic purposes. In addition to this, they can also be used to reduce toxicity of a therapeutic drug. As nanoparticles are used in various purposes, but their use in cancer drug delivery is more because the drugs which are bound with nanoparticles are easily soluble and are able to penetrate deep in organs and tissues. That is why nanoparticles are playing the key role to develop therapeutics against cancer. Also, these are used in fluorescent biological labels (diagnostic purpose), drug & gene delivery, detection of pathogens, detection of proteins, probing of DNA structure, tissue engineering, tumor destructive via heating (hyperthermia), separation & purification of biological molecules and cells, MRI contrast enhancement, phagokinetic studies etc. [49]. This review focuses on the synthesis and characterization of silver nanoparticles using natural plant extracts for the treatment of cancer. Silver (Ag) is a noble metal and it is applicable in medicines due to its unique properties [50]. As there are varying methods like soil-gel process, chemical precipitation, reverse micelle, hydrothermal method and biological methods, etc. are used to synthesize silver nanoparticles (SNP) but biological methods are ecofriendly, cost effective and don't involve the use of toxic chemicals [51], [52], [53]. SNPs are synthesized from different medicinal plants and are applied in pharmaceutical & biological field [54]; [23]; [55]; [13]; [14]; [56].

Applications of plant mediated synthesized silver Nanoparticles as anti-cancer therapeutics:-

Rapid synthesis method of silver nanoparticles using fruits, leaves, seeds and root extract of *Citrullus colosynthis* was evaluated against four different human cancer cell lines of different origin (ref). The cell lines used in this study are MCF-7 (Breast carcinomas), HepG2 (hepatocellular carcinomas) and Caco-2 and HCT-116 (Colon carcinomas). Silver nanoparticles characterization was performed using UV-Vis spectroscopy and TEM analysis. It was found that the nanoparticles are of irregular shapes with an average size 562.4 nm, but the average mean size of silver nanoparticlesof different parts of *C.colocynthis* like friuts, leaves, seeds and roots were 19.267 nm, 16.578 nm, 13.376 nm, 7.398 nm respectively. The cell viability assay of these silver nanoparticles on human cancer cells showed that Hep-G2 cell line and HCT-116 cell line were the most sensitive cell line with IC-50 21.2 µg/ml, 22.4 µg/ml where as Caco-2 cell line was the most resistant cell line towards cytotoxic activity (mention IC50) [52]. Silver nanoparticles synthesized with *Origanum vulgare* extract were tested by using leaves against human lung cancer cell A549, where IC50 was achieved at 100 µg/ml. In this study the silver nanoparticle size was characterized with UV-Vis spectroscopy where the size of silver nanoparticles was found to be 63-85 nm [53]. Another plant *Sesbania grandiflora* was used to synthesize silver nanoparticles from its leaves and its anticancer effect was tested against human breast cancer cell line MCF-7 with IC50 20 µg/ml. The size of silver nanoparticles was 22 nm confirmed by using UV-Vis spectral analysis and scanning electron microscope (SEM) [54]. Biosynthesis of silver nanoparticles was performed using *Cissus quadrangularis* due to its earlier reported antimicrobial and anticancer activity. It was observed that the size of silver nanoparticles after characterizing with UV-Vis spectroscopy and TEM to be 5-30 nm. The stem part was used to extract silver nanoparticles and its anticancer effect was studied against human liver cancer cell line Hep-2 with IC50 64 µg/ml [62].
The aqueous extract of marine micro-algea seaweed *Ulva lactuca* was used to synthesize silver nanoparticles and tested against human cancer cell lines Hep-2, MCF-7, HT-29 due to its earlier reported antibacterial, antiviral and anticancer activity. After synthesis of silver nanoparticles it was monitored by UV-Vis spectroscopy, Fourier transmission infrared (FTIR) and X-ray diffraction(XRD) analysis. The size was found to be 20-56 nm. Then the above cancer cell lines proliferation was inhibited by silver nanoparticles with IC50 12.5 µg/ml, 37 µg/ml and 49 µg/ml respectively [63]. The development of reliable and ecofriendly process for the synthesis of silver nanoparticles from *Brassica oleracea* was performed to check the anticancer effect against MCF-7. The whole cauliflower florets were used to obtain a size of 48 mm silver nanoparticles as characterized by UV-Vis spectroscopy, FTIR, XRD and SEM.These silver nanoparticle was found to inhibit the growth of MCF-7 cell proliferation with the IC50 value 190.501 µg/ml [64]. Aqueous extraction of seaweed *Gelidiella sp.* was used to synthesize silver nanoparticles where the size of that nanoparticle was determined to be 40-50 nm followed by using UV-Vis spectroscopy, energy dispersive spectroscopy (EDS), Fourier transmission infrared (FTIR) and scanning electron microscopy (SEM) analysis. Then the silver nanoparticles were used to evaluate cytotoxic activity of human cancer cell line Hep-2 and as the cancer cell line was significantly inhibited with Ic50 value of 31.50 µg/ml [65]. From table 2 it can be observed that SNPs from aqueous exracts of fruits and roots of *C.colosynthis* and seaweed *Ulva lactuca* extracts against Hep-G2 are the most effective in terms of anticancer activity in breast and liver cancer cells. But the aqueous extracts from *Origanum vulgare* and *Cissus quadrangularis* plant shows non-significant effect against cancer cell lines.

Future prospectives

The synthesis of silver nanoparticles using plant extract is an important aspect of nanotechnology and the applications of nanoparticles in various sectors. Green synthesis of nanoparticles are not time consuming compared to other biological process [66]. According to world health organization (WHO) the second leading cause of death in the world is cancer. As cancer is abnormal type of tissue growth, cell divisions occur rapidly in an autonomous fashion [67].

CONCLUSION

Biological synthesis of silver nanoparticles in nano-biotechnology area has increased its importance to create eco-friendly; cost effective, stable nanoparticles and their applications in medicines, agriculture and electronics are wider. From variety research on nanotechnology for synthesis of silver nanoparticles it is found that it is safer and better by using natural plants. With the huge plant diversity much more plants are still not explored for the synthesis of nanoparticles and its applications in pharmaceutical and agricultural industries.

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