Chapter 12
Green Synthesis of Metallic Nanoparticles and Applications in Biomedical and Environmental Research

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1 Introduction

Nanotechnology is one of the emerging fields used to produce interatomic structural particles. Nanoparticles are small in size (1–100 nm) and these particles exhibited wide application in medical, agriculture, chemical electronic, and pharmaceutical fields. The synthesis of NPs with predetermined morphology is the important objective in the fields of chemistry that can be used for the preparation of biosensor, biomedical, catalysis, and lower cost electrode. Nanoparticles have unique functional properties, and these NPs have specific characteristics of bulk materials. Hence NPs are the ideal materials for various uses in biotechnology, medicine, wastewater treatment, and preparation of health care products. Many methods have been applied for the fabrication of NPs with predetermined properties. Although these methods have resulted in NPs with desired properties, still a basic knowledge of the high-quality fabrication is essential that could be effectively utilized at industrial levels for bulk manufacturing. To prepare NPs, two basic approaches (bottom-ups and top-down) are used. Conventionally, NPs are prepared by using various methods, such as sputtering, etching, ball milling, and lithographic techniques [4, 10]. The use of the bottom-up approach method involves many steps, including, sol–gel process, atomic condensation, vapor protocols, and spray pyrolysis. Green synthesis methods of NPs preparation attained much more attention in recent years and are presently used in current research and development on materials science. These green synthesized NPs reduce environmental pollution; reduce the utilization of toxic-solvents, prevention of waste, and eco-friendly. Biosynthesis is one of the important approaches to use biological materials and avoid toxic by-products using sustainable and eco-friendly

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method. Green synthesis of metal and metal oxide NPs has been adopted to accommodate many sources, including, bacteria, algae, and plant extract [24]. The application of plant extract is a simple, rapid, and easy method to obtain NPs in large quantities than bacteria, plant, and fungi-based NPs synthesis. Biosynthesized NPs have several applications in the pharmaceutical industries such as synthesis of functional nanodevices, drug delivery personification procedure. These NPs have various applications in industries, including wastewater treatment, in the preparation of pharmaceuticals, synthesis of functional nanodevices, and drug delivery personification procedure [17, 23]. In this chapter we summarize the present research on the green synthesis of ZnO NPs and their applications. The main objective of this chapter was to promote green synthesis of ZnO NPs using plant extracts form biomedical and environmental applications.

2 Green Chemistry in Nanoparticles Biosynthesis

Green chemistry is widely used to produce NPs using biological samples. Chemical synthesis of NPs was achieved with the generation of hazard materials and many methods have been suggested to reduce the hazards to the environment. The sustainable and safe approaches and analysis support to reduce health hazard to the animals and the environment. Green chemistry is one of the newly emerged fields in chemistry. Green chemistry has potential role in the sustainable development that emerged for the fulfillment of present-day requirements and for future generations [46]. Green chemistry has specific role in sustainable development and has unique importance because of its application in pollution control and the application of naturally available resources [1].

3 Green Synthesis of Metal and Metal Oxide Nanoparticles

Plants, fungi, bacteria, actinomycetes, and algal samples are commonly applied for the biosynthesis of NPs. These extracts/samples have novel therapeutic properties and are applied for the biosynthesis of NPs with desired biological properties. In biological synthesis, both unicellular and multicellular organisms are applied in green chemistry [36]. Among various natural sources, plants are one of the major bioresources of natural environment that are eco-friendly and inexpensive. Algae, fungi, bacteria, and actinomycetes extracts are used for the green synthesis of NPs, moreover, the application of plant extract to produce NPs has several advantages. In plants, root, fruit, leaf, stem, bark, flower, and seeds have various phytochemicals, and these phytochemicals have the ability to reduce NPs. The selected plant parts are processed using sterile water and used as a reducing agent. The color of the salt solutions begins to change after the addition of plant extract and this color change reveals the synthesis of NPs.

4 Plant Extract is a Natural Capping Agent

Plant extract is widely used as the natural capping agent for the biosynthesis of NPs production. These natural capping agents are applied to maintain functional properties and to stabilize NPs. Capping agents are used to produce NPs with desired morphology. Generally, surfactants have used as the capping agent to achieve desired properties. However, these chemical capping agents are highly toxic to the environment and very difficult to remove. Due to these drawbacks, alternate capping agents are essential to form NPs with desired particle sizes. The phytochemicals of the medicinal plants serve as stabilizing agent and some of the phytocompounds acting as capping agent. In recent years, plant-mediated NPs synthesis was performed using various medicinal plants [29]. Plant phyto-components such as terpenoids, flavonoids, phenolic compound, protein, and amino acid are used for the biosynthesis of NPs. Isoprenoids or terpenoids have applied for the biosynthesis of iron NPs. These terpenoids are important secondary metabolites of the terrestrial plants. Terpenoids are also used for the preparation metal NPs [58]. Sesquiterpenoids and monoterpenoids are the two important terpenoids used for the biosynthesis of silver NPs [54]. Flavonoid is one of the phytochemicals in plants and this pigment is widely distributed among plants. About 7000 flavonoids are reported and are available in various forms such as, isoflavones, flavanol, flavones, anthocyanidins, flavanones, and flavan3-ol. Flavonoids are primarily considered as one of the widely distributed plants based reducing substances and their bio-reducing property and donate electrons. Phenolic acid including gallic acid, ellagic acid and protocatechuic acid are used as reducing agent for the green synthesis of NPs [3]. Polysaccharides are used as the reducing agents and widely used in green chemistry. These polysaccharides modify the shape, size, and structure of TiO_2 and induced various phases. For example, rutile phase is obtained in the presence of chitosan in the medium and starch is used to generate anatase phase. Green synthesis offers the use of nontoxic substances for the extraction of phytochemicals [16]. Natural polysaccharides improve the kinetics of sol–gel methods because of their potent catalytic properties and have been reported previously [9]. Amino cellulose is used for the synthesis of gold nanoparticles and acted as reducing and capping agent. Amino acids are useful for the preparation of NPs with smaller particle size (4–7 nm). L-histidine is used for the preparation of gold NPs and the concentration of amino acid decides the particle sizes [35].

5 Synthesis of ZnO Nanoparticles Using Plant Extract

Root, bark, seed, peel, stem, and leaves are applied for the preparation of ZnO NPs. Walnut extract has been recently used to produce ZnO NPs [48]. The phytochemicals extracted from *Cayratia pedata* are used to produce ZnO NPs [26]. Plant phytochemicals extracted from the root are used in the preparation of ZnO NPs.

Dimethyl sulfoxide extract of *Rubus fairholmianus* has the potential to produce ZnO NPs and the average particle size was approximately 10–12 nm [44]. *Phoenix dactylifera* is applied for the green synthesis of ZnO NPs [39]. Flower contains various pigments and the biological action of these pigments mediated ZnO NPs. *Cassia auriculata* extract is applied for the generation of flake structured ZnO NPs [61]. *Punica granatum* flower synthesized ZnO nanoparticles with excellent properties [41]. The aqueous flower extract of *Moringa oleifera* is evident in the presence of bioactive secondary metabolites and these compounds mediated ZnO NPs with 13–14 nm [45]. A hexagonal and triangular-shaped ZnO NPs with 30–40 nm size was obtained with *Syzygium aromaticum* extract [60].

6 Antibacterial Activity of ZnO Nanoparticles Against Drug Resistant Bacteria

Zinc oxide NPs have antibacterial activities and the NPs caused ROS-mediated cellular toxicity and membrane damage. They are bioactive potential against drug resistant bacteria, including, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Bacillus megaterium*, *Bacillus subtilis*, *Sarcina lutea*, *Aspergillus niger,* and *Candida albicans* [27, 34, 50]. Walnut aqueous leaf extract mediated ZnO nanoparticles showed activity against multi-drug resistant *E. coli*, *S. aureus,* and *E. coli* [48]. The aqueous extract of leaves from *Lippia adoensis* mediated ZnO NPs was effective against bacteria such as *Escherichia coli*, *Klebsiella pneumonia*, *Staphylococcus aureus,* and *Enterococcus faecalis* [14]. Piper betle-mediated ZnO NPs show potential antibacterial activity against *S. aureus* and *E. coli* [56]. *Arthrospira platensis* leaves extracted with fabricated ZnO was effective against bacterial strains such as *S. aureus*, *B. subtilis* and the increased activity was observed at higher concentrations. At lower concentrations of ZnO antibacterial activity decreased [18]. The ethanol extract of *Sambucus ebulus* mediated ZnO nanoparticles have antibacterial activity against various human bacteria. *Anacardium occidentale* mediated ZnO nanoparticles showed activity against drug resistant pathogens such as *A. Baumanii*, *E. coli*, *K. pneumoniae*, *E. aquaticum,* and *S. aureus* [15]. *Punica granatum* flower extract has effectively mediated ZnO NPs biosynthesis and was effective against bacteria such as *K. pneumoniae*, *P. aeruginosa*, *B. cereus*, *S. aureus*, *S. diarizonae*, *E. faecalis*, *E. coli*, *L. monocytogenes*, *A. hydrophila*, *E. faecium*, *M. catarrhalis,* and *A. hydrophila* [25].

7 Mechanism of Action of ZnO on Microorganisms

ZnO materials have antimicrobial properties, and the mechanism of action is based on adsorption, Zn^{2+} ion release, generation of reactive oxygen species, and intracellular energy metabolism inhibition, cell membrane damage, lipid peroxidation, DNA breakage, and DNA replication disruption [32]. ZnO NPs/MPs release Zn^{2+} ions and it induced an antimicrobial response against various pathogenic bacteria due to inhibitory effect in enzyme system and in metabolic processes. The surface of ZnO NPs/MPs (positively charge) effectively interacted with the bacterial cell wall (negatively charge) [22]. After adsorption, the microorganism losses its integrity, membrane rupture or cell wall, and induced oxidative stress owing to lipid peroxidation reaction and damage DNA. ZnO NPs have different specificity against bacterial pathogens, influenced by their physicochemical properties such as porosity, morphology, surface charge, and particle size [22]. ZnO NPs/MPs have multiple functions than other NPs prepared from metals. The antibiotic metals namely, gold and silver NPs have the principal function of membrane adsorption, and metal ion release. The other particles such as cupric oxide, titanium dioxide, and magnesium oxide NPs show NP internalization, ROS generation, and induce damage to bacteria. ZnO NPs/MPs effectively combat bacterial growth and prevent the development of antibiotic resistance and NPs penetrate the bacterial cell [28].

ZnO NPs combined with other metal NPs showed considerable antibacterial activity against virulence hospital pathogens. The synergistic bioactive materials improve sustainability and have repeat usability in various biomedical applications, then ZnO NPs alone. These particles combined with ZnO NPs/MPs improved activity against bacterial strains and overcome antibiotic resistance. Metals doped with polymers, polyhydroxyapatite, carbon-based material, graphene oxide, quantum dots, and reduced graphene oxide [51]. They improved synergistic microbial inhibition or involved the antibacterial pathways of ZnO NPs in bacteria to inhibit bacterial growth or create synergistic properties.

8 Antifungal Activity of ZnO Nanoparticles

ZnO NPs are ionic metal oxides that have unique properties such as unusual crystal structures and high surface area. Inorganic materials such as ZnO show greater selectivity, superior durability, and heat resistance. However, zinc is one of the important mineral elements required for human health in the form of ZnO [21]. ZnO NPs have antifungal properties and zinc compounds are widely used as fungicides. The antifungal activities of ZnO NPs are based on the development of free radicals on the surface of the ZnO NPs and break down of the cell membranes. Zinc oxide NPs induced ROS-mediated cellular changes and membrane damage. They are highly effective against fungal species such as *Aspergillus niger* and *Candida albicans.*

The commercially available antifungal agents have very limited applications. Consequently, the inorganic antifungal agents cause serious side effects such as renal failure, liver damage, diarrhea, nausea, increased body temperature after drug consumption. The plant-mediated iron or iron oxides NPs can damage fungal hyphae and effective against spore-forming fungal strains. The metal and metal oxide NPs interact with fungi cell membrane and structure and affect membrane structure and function [30].

9 Antioxidant Activity

Nanoparticles have antioxidant activity and these NPs involved in various biochemical reactions. These antioxidants have scavenging of free radicals, production of reactive oxygen species, and changing intracellular redox state [20]. Reactive oxygen species generation is involved in various diseases including, Alzheimer's-, Parkinson's-disease, and various neurodegenerative disorders. The generated free radicals in the biological system effectively cleave hydrogen bonds in DNA macromolecule and affect the base pairs of DNA, which can mediate in the development of types of cancers. Cancer disease is one of the leading causes of death throughout the world and the current radiation therapy and drugs affect the normal cells. Antioxidant molecules have potential anticancer activities and may effectively reduce various types of toxicity linked with chemotherapy treatment [31]. Hence, the application of antioxidant from natural sources during treatment shows an adjunct for the treatment of various types of cancers. There are various drugs used to treat cancer, moreover, these drugs involved unexpected side effects [12]. ZnO NPs are applied in the textile and rubber industries [57]. ZnO nanoparticles show 1-diphenyl-2-picryl-hydrazyl (DPPH) free radical scavenging antioxidant activity [12]. Medicinal plants extract mediated NPs have antioxidant potentials. *Polygala tenuifolia* root extract mediated ZnO nanoparticles show antioxidant activity [40, 52].

10 Anticancer Activity

Cancer disease is the emerged diseases and consists of about 100 types of cancers. Cancer cells are characterized by unrestricted cell division of cells with abnormal characters. The number of cancer cases increased in recent years. It is estimated about $150 billion in 2020 [6]. Nanomedicine is one of the emerging fields and attained much more attention for the treatment and diagnosis of cancers. Nanomedicine shows potential characteristics based on phytochemicals involved in the formulations of metal nanoparticles. The plant-mediated NPs have attracted increased attentions for cancer treatment. The NPs have unique physical, optical, electrical, and the properties may vary based on the surface volume, charge, particle size, and other functional properties. Nanomedicine is one of the fast-expanding research areas of nanoscience and mainly metallic NPs have applications in the synthesis of nano-platform drugs because of unique physicochemical activities. Moreover, the biogenic metallic nanoparticles have potential applications in the treatment of cancer. Medicinal plant extract has been applied for the preparation of anticancer ZnO NPs [30]. These metallic NPs have fluorescent properties when exposed to X-rays. It can be used to diagnose cancer cells in the human body. In recent years, various therapeutic molecules and strategies were applied for the treatment of cancer at various stages of development. Moreover, most of the commercial drugs have least specificity against cancer cells and induced toxicity to the normal cells. These drugs show least stability, low degradation potential from the biological system, and poor targeting ability. FDA approved nanomedicine for the preparation of cancer treatment. Onivyde (80 and 140 nm), NanoTherm iron oxide NPs (20 nm) are used to treat metastatic pancreatic cancer and for thermal ablation of glioblastoma.

Anticancer properties of ZnO NPs (10 nm) Hela cell lines were studied at various NPs concentrations. ZnO NPs showed dose-dependent anticancer activity and the cell viability reduction was 5–50% in HeLa cells. Fe-doped ZnO NPs and ZnO NPs are quasi-spherical in shape and the synthesized particle size was approximately 10–20 nm in size and showed anticancer activities [42]. The chitoson-coated NPs are spherical shaped and 100 nm in diameter. These chitosan-coated and uncoated materials were tested against Hela cells at various concentrations [11]. The chitosan-coated Hela cells improved cytotoxicity through cellular internalization, formation of ROS, apoptosis, and cell death at 75 μg/mL concentrations. The green synthesized ZnONPs mediated by the aqueous extract of *Gracilaria edulis* showed cytotoxicity [19].

11 Pesticidal Properties

Nanoparticles penetrate through plants cells hence they become to act as nanocarriers making them more efficient in targeting the plant pests. The nanoparticles such as CuO, Ag, ZnO, and MgO have potent insecticidal activity against various pests. ZnO has a lot of potential against various pests than other oxides. Metal NPs have toxic effects, and it effects on crustaceans, plant pests, and bacteria. NPs are effective against pests from different orders including, *Lepidoptera*, *Coleoptera*, *Diptera*, *Hemiptera*, Nanoparticles such as gold, silver, aluminum, zinc, silica, zinc oxide, metal oxide, and titanium dioxide are useful to control pests [47, 55]. Silica nanoparticles are also applied to control insect pests [13]. Nanoparticles induce desiccation in larvae and decreased cell viability. Silica microparticles affect *T. molitor* larvae and induced mortality and the mortality rate was about 70%. Silica microparticles damage dermal and epidermal cells of larvae which lead to dehydration of the larvae and become dark [7].

12 Photocatalytic Degradation of Organic Dyes

Organic dyes are one of the important pollutants causing negative effects on the environment. Organic dyes are very stable, toxic, resistant, and carcinogenic compounds. These are applied in the food, plastic, textile, and leather industries. The textile industry involves the maximum levels of water pollution due to organic dyes. The existence about 10,000 colorants has been introduced, of which about 700,000 tons are discharged in every year [49]. The methods such as adsorption, reductive reaction, Fenton reaction, and biodegradation are useful [43]. Moreover, some of these described methods are highly expensive, required toxic chemicals, and affect the eco-system and the environment. Among these techniques, photocatalytic method is a low-cost, simple degradation, and harmless. This method is useful in removing various pollutants in wastewater and aquatic system using UV energy or solar energy. The green synthesized silver NPs and zinc oxide nanorods composite was effective to degrade 92% of paracetamol in water within 4 h of incubation [2]. Photocatalyst is used in photocatalytic process, and this is generally a semiconductor substance that, by effectively absorbing photons from the water, is generally activated to generate hydroxyl radicals and thus uses the complete organic dye degradation [59]. The semiconductors such as, tin dioxide (SnO_2), titanium dioxide (TiO_2), iron oxide (III) (Fe_2O_3), copper oxide (CuO), and ZnO are widely used as photocatalysts [8, 37]. ZnO is widely applied in sensor, batteries, solar cells, and ZnO is considered as one of the super catalysts in the removal of pollutants from the wastewater. ZnO NPs have good oxidizing potential and show a bandgap of approximately 3.37 eV, excellent mechanical and chemical stability, photosensitive property, leading to various environmental applications [53]. *Camellia sinensis* extract is useful for the green synthesis of SnO_2 NPs with the particle size between 4 and 5 nm [33]. Lemon peel extract was used to green synthesize TiO_2 NPs and it was quasi-spherical shape, and the size was between 80 and 140 nm [38]. *Allium sativum* extract was used for the green synthesis of CuO NPs and the particle size ranged between 20 and 40 nm [33]. These green synthesized NPs have potential application in the degradation of various organic dyes. The NPs prepared using Jasmine powder showed MB degradation activity and 78% degradation was achieved within 2 h [5]. Camellia sinensis extract was used for the synthesis of iron NPs and is applied for the degradation of MO from the wastewater.

13 Conclusion

Metal and metal oxide NPs have been widely used in the field of environment and health sciences. Thus, the chemistry of green synthesis and the application of the synthesized NPs are important for various applications. Green synthesis uses extracts from bacteria, fungi, algae, and plants. Moreover, plant extracts have remarkable efficiency in reducing, capping, and stabilizing agents than other sources for the preparation of nanoparticles with desired molecular properties due to the presence of capping agents and reducing power. This chapter shows the use of plants for the green synthesis of nanoparticles and covers the application of nanoparticles for biomedical and environmental applications. The antibacterial, antifungal, anticancer, and antioxidant power of the nanoparticles were described. ZnO is a semiconductor that has excellent thermal stability and is widely used as sensor, luminescent material, batteries, solar cells, optoelectronic applications and is considered as one of the super catalysts in the removal of pollutants from the wastewater.

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