



## Synthesis of nanoparticles using biological entities: an approach toward biological routes

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### ABSTRACT

Nanoparticles (NPs) have received worldwide attention due to their utilization in various fields such as medicine, biosensors and pharmaceuticals. Biological resources such as bacteria, fungi, algae and plants have been proved to produce several types of NPs with numerous shapes and sizes. Biological resources are being investigated to reduce the effects of hazardous chemicals and reducing agents used in the synthesis of NPs, since the biological resources act as reducing and stabilizing agents. Conventional methods such as chemical and physical syntheses involves hazardous chemicals which later become a concern for health and the environment owing to their toxicity. The expansion in green route for effective metal-based NPs synthesis by using biological resources is a captivating research area in nanotechnology as they have positive economic and eco-friendly significances in comparison with the chemical and physical methods. The synthesis of NPs using plant extract is the most suitable method compared to using bacteria, fungi and algae, as it requires less energy, is safe and can be easily scaled up. These advantages are most desirable for wound healing, antibacterial, antifungal, anti-inflammatory and antidiabetic applications. Therefore, the current paper aims to review the synthesis of NPs using bacteria, fungi, algae and plants and their potential applications in different fields.

*Keywords:* Biosynthesis; Green nanotechnology; Reducing/stabilizing agent; Metal nanoparticles

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### 1. Introduction

Researchers around the world are discovering the novel aspects of nanotechnology due to rapid evolutions and technological modernization in science and technology. Nanotechnology is the ability to control matter at the supra-molecular level (1–100 nm) [1]. Nanotechnology is attaining modernization in a massive number of fields such as biomedical, health care, catalysis, cosmetics, nanodiagnostics and antimicrobials [2,3]. There are several types of nanoparticles (NPs) such as metallic, metal oxide, alloy-based and magnetic NPs [4]. NPs made from gold (Au), nickel (Ni), silver (Ag),

iron (Fe), zinc oxide (ZnO), platinum (Pt), palladium (Pd) and titanium dioxide (TiO<sub>2</sub>) have been widely produced for various applications. For example, Pt and Ag NPs are widely used in cancer treatment; Au NPs are used as a biosensor in detection of the chemical and biological substances in disease diagnoses, electrochemical devices and environmental protection [5]; Pd NPs are used in optoelectronics; and ZnO NPs are used as coating materials and in cosmetics fields [6]. Moreover, utilization of NPs in chemotherapies and radiotherapies reduces the side effects of the treatment [7]. This is due to NPs' ability to act as both carriers and substrates for bioactive compounds, different ligands, probes for imaging,

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thermal and radiotherapy and, simultaneously, they can be effectors by themselves [8]. The main challenge in synthesizing NPs is the production of NPs with a preferred composition, well-defined size, specific shape and controlled dispersity, which control their physical, chemical, catalytic, electrical, optical, magnetic and electronic properties [9]. The NPs' size, shape, and stability are affected by growth parameters such as pH, temperature, exposure time and concentration of stabilizing agent as described in Sections 2.1, 2.2, 2.3, and 2.4, respectively [10].

NPs are synthesized by top-down or bottom-up techniques (Fig. 1). The breakdown of larger organic or inorganic materials to small molecules is known as the top-down approach. On the contrary, tiny molecules produced by self-assembly are known as the bottom-up approach [11]. The disadvantage of top-down method is the imperfection in NPs surface, which causes severe constraint as the surface structure of the NPs plays an important role in physical properties and surface chemistry of NPs, whereas bottom-top method generally depends on chemical and biological procedures [6]. There are three routes for the synthesis of NPs: chemical synthesis, physical synthesis and green synthesis. Chemical synthesis includes liquid ultrasonication, chemical vapor deposition, solvothermal method, sol-gel, sonochemical method and microwave, which involve inorganic and organic chemicals accompanied by strong reducing reagents and solvents while physical synthesis comprises sputtering, laser ablation, ball milling and beam epitaxy, which demand high pressure, temperature and consumption of energy [12,13]. Chemical and physical methods are mostly involve more than one chemical type and may increase the reactivity and toxicity of the NPs, which can damage the environment and human health owing to the uncertainty in composition and lack of predictability [10]. Moreover, physical procedures require a long time to reach thermal stability and they increase the environmental temperature near the source material [4]. Furthermore, development of these methods for large-scale productions is limited because of high preparation costs resulting from great energy consumption, use of toxic organic solvents, production of hazardous intermediates, and formation of dangerous waste products that cause

environmental pollution [9]. In addition, the current NPs production techniques produce up to 100,000 kg waste per kg product, which is up to 1,000 times more wasteful compared to the waste production of pharmaceuticals and fine chemicals [14]. The high productions of NPs clearly stress the urgent need for new NPs production designs that are green and sustainable.

Currently, green synthesis is the hottest topic in the production of metal NPs as it reduces the pollution risk at source level and the approach avoids waste rather than treating waste after it is produced. This way is superior, safer, nature-friendly, and involves biological materials which include plants, bacteria, yeast, and algae [15]. Pollutant-free chemicals are widely employed in green/biological synthesis during the preparation of NPs. Eco-friendly and safe solvents such as water and natural extracts are exploited in the process of green synthesis [16]. Hence, the generated NPs are free of toxic chemicals and are eco-friendly. Biological synthesis has gained attention globally not only because of its reduced environmental impact compared with physical and chemical procedures, but also because it generates huge quantities of NPs that are free of contamination and with well-defined size and shapes [17]. Furthermore, biological entities are able to act as templates in the synthesis, assembly, and organization of nanomaterials to fabricate well-defined micro- and macroscale structures. Both microorganisms and plants have the potential to absorb and accumulate inorganic metallic ions from their surrounding environment [18]. Biological entities possess natural capping and stabilizing agents, which are required as a growth terminator and prevent aggregation or agglomeration. The possible mechanism of NPs synthesis by green technique is illustrated in Fig. 2. Biological molecules such as sugars, proteins, enzymes, and even whole cells that stabilize NPs effortlessly allow NPs to interact with other biomolecules. This consequently increases the antimicrobial activity by enhancing the interactions with microorganisms [10]. Biological techniques are expected to reduce the cost of the raw materials, guaranteeing long-term sustainability by decreasing energy and waste, if the techniques are scalable for industrial production [14]. Furthermore, utilization

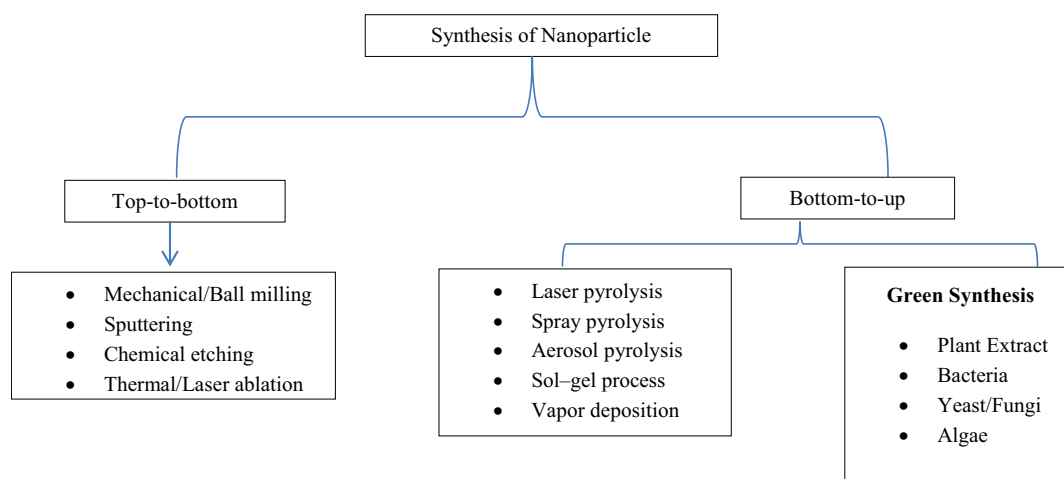


Fig. 1. Routes to synthesize nanoparticles.

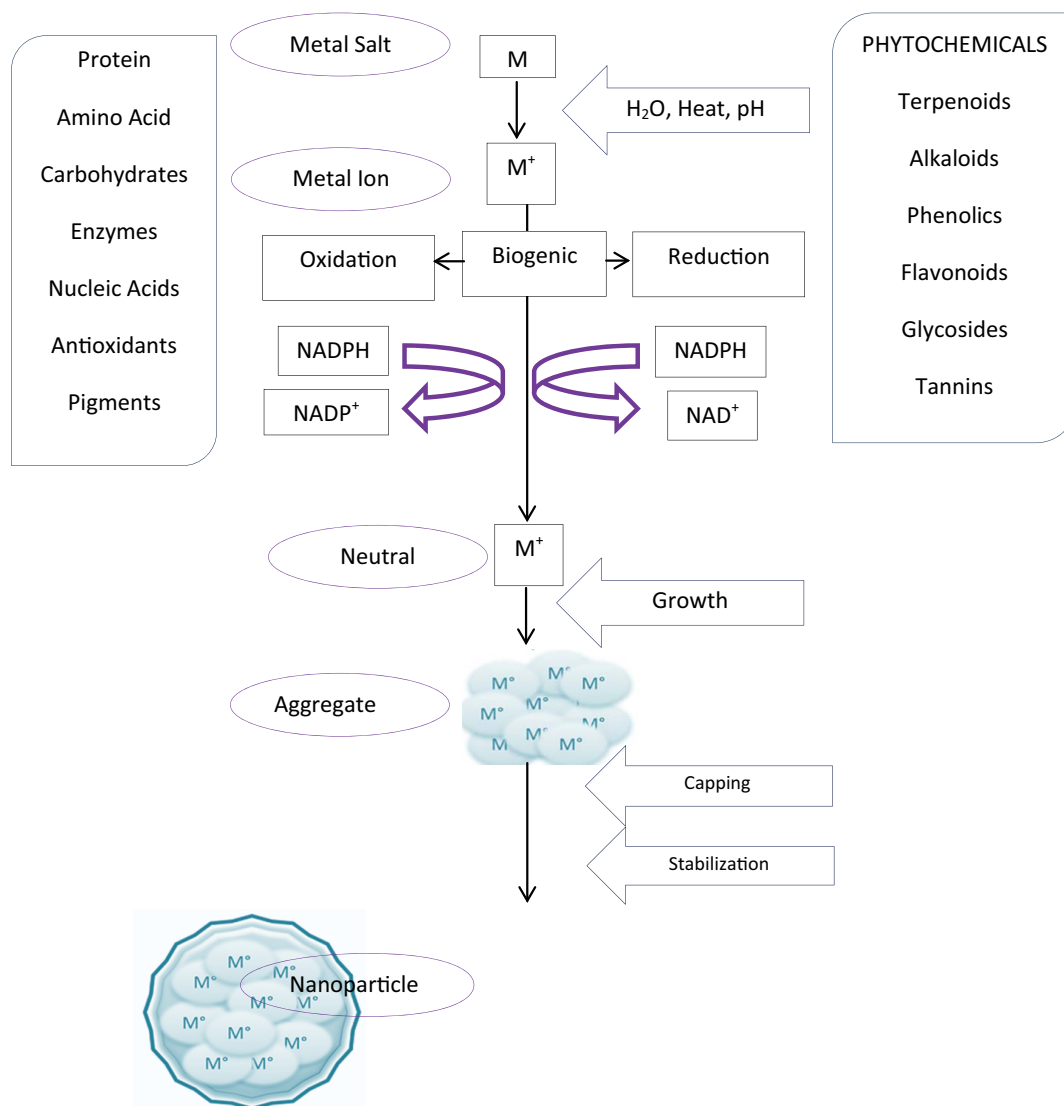


Fig. 2. Summary of possible mechanism of green mediated synthesis of NPs. M: metal salt,  $M^+$ : metal ion,  $M^\circ$ : neutral atom (adapted from [10]).

of living organisms is beneficial for drug delivery, pharmaceutical, diagnostics, medicine, agricultural practices, environmental biotechnology, and biosensing [1]. Green nanotechnology is also advantageous in the energy sector such as batteries, fuel, and solar cells, which are more effective with this technology [19]. However, few studies have highlighted the advantages of green nanotechnology and its applications in real industries. Thus, the main aim of this review is to highlight the types of biological entities employed in green synthesis and their applications.

## 2. Factors affecting the growth of NPs

### 2.1. Effect of pH

The pH of the solution during the synthesis affects the size and shapes of NPs [20]. This is due to the development of nucleation centers, which increases when the pH

increases. Thus, the reduction of metallic ion to metal NPs also increases [21]. Charge transformation occurs in the synthesis of NPs during the pH adjustment in the plant metabolite which consequently affects its capacity to degrade the metal ions throughout the process, altering the morphology, size, and yield of NPs. Moreover, pH has an effect on the electrical charges of biomolecules, which influence their growth, capping, and stabilizing abilities [9]. Thus, formation of NPs of desired morphology at certain pH range with better stability can be achieved [22]. As the pH decreases, the reducing power of different functional groups in biological entities also decreases, owing to the high  $H^+$  concentration in the aqueous phase. Contrarily, when the pH increases, the reducing power of the functional groups also increases, inhibiting aggregation of metal NPs. This is because the hydrophilic and hydrophobic interactions of intramolecular forces prevent the aggregation of metal NPs and thus

increase their stability. [23]. Briefly, it can be concluded that larger particles are produced at lower pH [18].

### 2.2. Effect of temperature

Temperature plays an important role in the synthesis of metal NPs by influencing the shape and size of the NPs [4]. High temperature assures enhanced crystallinity of NPs with high rate of nucleation [9]. Formation of nucleation centers increases as the temperature increases, which consequently increases the biosynthesis rate [21]. Moreover, it has been stated that an increase in temperature can cause an increase in the intensity of the surface plasmon resonance (SPR) due to bathochromic shift, causing the size of NPs to decrease [24]. Sharpness in absorbance peak indicates the formation of smaller NPs [25]. This is because an increase in the temperature causes changes in the kinetic reaction, the atomic movement in the solution (Brownian movement) and the mechanisms of aggregation of the NPs [26]. Contrarily, at low temperature, the intensity of SPR peak decreases and the width of the SPR band broaden, indicating that fewer NPs are formed and the size of the particles are bigger [27].

### 2.3. Effect of exposure time

The duration of incubation for NPs reaction media significantly influences the quality and shape of the NPs produced. Extended NPs incubation can cause agglomeration which can cause a reduction in the NPs' capability [20]. Besides that, when the reaction time increases during the synthesis of NPs, the intensity of the SPR peak increases. This indicates an increase in the number of NPs formed in the mixture [27]. A stable and narrow shape of the SPR can be observed as the reaction time increases and optimum time is reached during the synthesis of NPs [24].

### 2.4. Effect of stabilizing/reducing agent

Different plants have different reduction capabilities which influence the synthesis of NPs. For instance, tryptophan and amino acids are strong reducing agents among phytochemicals and thus they are able to reduce a large amount of metal ions in a short time [9]. Similarly, different microorganisms produce various intracellular and extracellular enzymes which influence the synthesis of NPs [20]. In brief, the presence of reducing and stabilizing agents decides whether these metal precursors could be reduced and leads to the NPs formation. Hence, the type and concentration of the plant extract/biomass or microorganisms used during the synthesis of NPs are essential as they control the amount of reduction and stabilization utilized by the phytochemicals, which affect the shape and size of NPs [22].

## 3. Green synthesis of metal NPs

Green synthesis of metal NPs involving biological entities such as bacteria, fungus, algae and plant extracts are described in detail in Sections 3.1, 3.2, 3.3 and 3.4 respectively.

### 3.1. Green synthesis of metal NPs using bacteria

Bacteria are ubiquitous in soil and water and they have been most extensively researched for the synthesis of metallic

NPs. The ability of bacteria to survive and grow in stressful situations such as in high concentrations of heavy metals is attributed to the inactivation and complexation of metals, the bacteria's impermeability to the metals, and the deficiency of particular metal transport systems [28]. The processes involved to produce inorganic materials by bacteria can be intracellular or extracellular [21]. Due to the benefits such as being cost-effective to grow, having high growth rate and unchallenging genetic manipulability, bacterial systems denote a suitable method for extracellular synthesis of metal NPs [29]. *Streptacidiphilus durhamensis*, *Bacillus mycoides*, *Pseudomonas aeruginosa*, *Phormidium tenue*, *Morganella morganii*, *Bacillus subtilis*, and *Aeromonas hydrophila* are examples of bacterial species that have been exploited for the synthesis NPs with various size and shape (Table 1). Bacteria are used in green synthesis owing to their ability to produce extracellular particle, ease of culturing and fast generation time [30]. Furthermore, this method is sustainable, biocompatible, nontoxic, easily used for mass production and cost effective [31]. Bacteria can able to convert the heavy metal ions into nontoxic forms due to their chemical detoxification and energy-dependent ion efflux from protein's cell membrane by ATPase or as chemiosmotic cation or proton anti-transporters. This increases their possibilities of survival in natural habitats [32]. In short, microbial systems are able to detoxify the metal ions by reduction and precipitation of toxic ions nontoxic metal nanoclusters [33].

Cyanobacteria are amongst the bacterial species which have been used for production of NPs, due to their high growth rate, biomass productivity, and production of water-soluble fluorescent pigments such as phycobiliproteins, which make them appropriate for biosynthesis of metal NPs [24,25]. The pathway for green synthesis of metallic NPs by cyanobacteria is illustrated in Fig. 3. NPs produced by individual actinobacteria show better polydispersity and stability and have good biocidal activity against numerous pathogenic microorganisms [30]. Moreover, the presence of enzymes in the cell wall of microorganisms has a great effect in degradation of toxic metals by bioremediation. For instance, *Bacillus* sp. is a good metal-reducing bacteria used for the removal of toxic metals such as cadmium (Cd), arsenic (As), lead (Pb), and zinc (Zn) [36]. Bacterial cells can easily adapt with heavy metals and consequently generate rare size and shape of inorganic NPs by intracellular or extracellular mechanisms [37]. Other than that, *Rhodococcus* spp. are suitable for biotransformation of several organic compounds as they have the potential to uptake and metabolize hydrophobic compounds and persist in adverse conditions [38].

### 3.2. Green synthesis of metal NPs using fungus

Formation of NPs by fungi occurs as a result of environmental stresses such as aqueous metal ions ( $\text{AgNO}_3$  and  $\text{AuCl}_4$ ) and temperature variations. The process happens both intra- and extracellularly to shield the fungi from undesired foreign substances by reducing the metal ions to metal NPs through the catalytic effect of the extracellular enzyme and metabolites of the fungus. Extracellular synthesis is faster compared to the intracellular passage; however, NPs synthesized through extracellular process are larger [18,29]. Fungi contain proteins, enzymes, and reducing components

Table 1  
Various metal NPs of different sizes and shapes synthesized from bacteria

Species	Nanoparticles	Size (nm)	Morphology	References
<i>Streptacidiphilus durhamensis</i>	Ag	8–48	Spherical	[30]
<i>Cylindrospermum stagnale</i>	Ag	38–88	Spherical	[34]
<i>Bacillus methylotrophicus</i>	Ag	10–30	Spherical	[67]
<i>Anabaena</i> sp.	ZnO	80	Spherical	[35]
<i>Bacillus mycoides</i>	TiO <sub>2</sub>	40–60	Spherical	[68]
<i>Bacillus licheniformis</i>	ZnO	250–1 μm	Flower	[69]
<i>Rhodococcus pyridinivorans</i>	ZnO	100–120	Quasi-spherical to hexagonal	[70]
<i>Pseudomonas aeruginosa</i>	ZnO	35–80	Spherical	[71]
<i>Microcoleus</i> sp.	Ag	44–79	Spherical	[72]
<i>Morganella morganii</i>	Cu	15–20	Quasi-spherical	[32]
<i>Bacillus subtilis</i>	AgCl	47	Spherical	[36]
<i>Aeromonas hydrophila</i>	ZnO	57.72	Spherical	[73]
<i>Bacillus cereus</i>	Ag	20–40	Spherical	[74]
<i>Phormidium tenue</i>	CdS	5	Spherical	[75]
<i>Lactobacillus casei</i> subsp. <i>casei</i>	Ag	25–50	Spherical	[76]
<i>Bacillus subtilis</i>	TiO <sub>2</sub>	10–30	Spherical	[37]
<i>Rhodococcus</i> sp.	Ag	10	Spherical	[38]

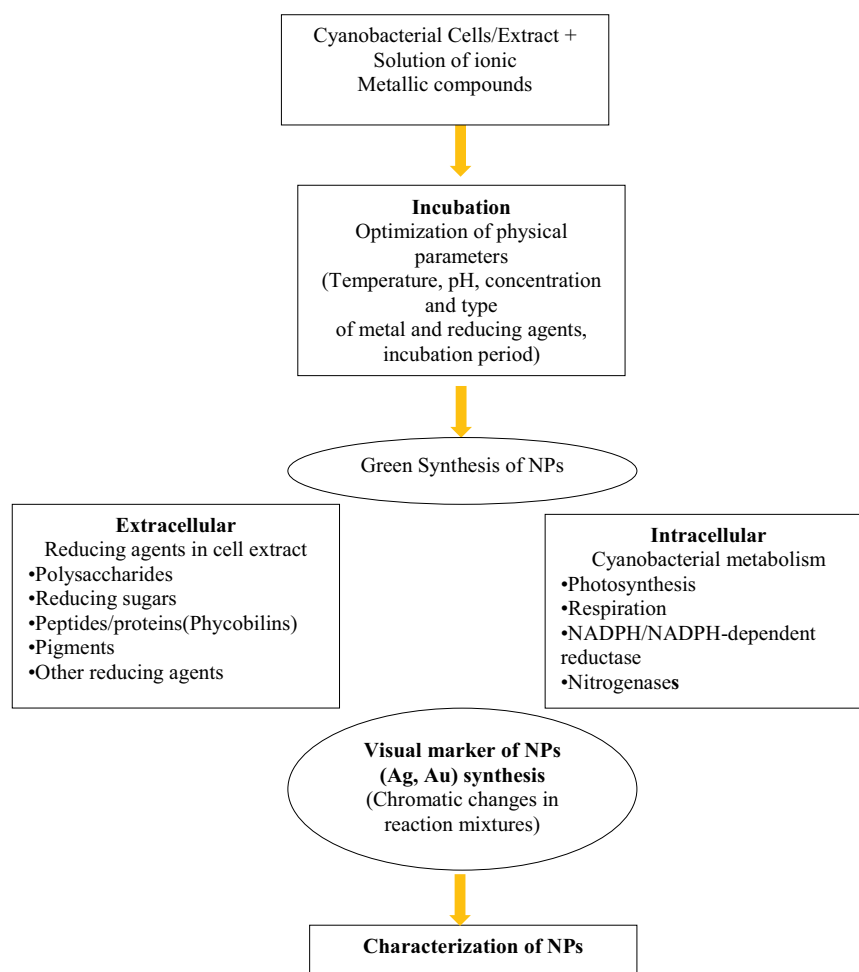


Fig. 3. Pathways for green synthesis of metallic NPs by cyanobacterial cell (adapted from [23]).

on their cell surface and produce reducing agents such as naphthoquinones and anthraquinones [40]. Utilizing fungi as the stabilizing/reducing agent is very effective in producing NPs with well-defined morphologies as they produce different types of intracellular enzymes for the development of metal and metal oxide NPs [41]. Since fungi have high binding capacity, tolerance, metal bio-accumulation ability, and intracellular intake, they are utilized to synthesize metallic NPs. Synthesis of NPs by fungi is more beneficial compared to other microorganisms as fungi are easy to isolate, their cultures grow faster than bacteria, and are easy to handle and produce in the laboratory. Fungi also can resist the flow pressure and agitation in bioreactors [4]. Moreover, the fungi's mycelia give a huge surface area for interaction and secrete significant amount of protein compared to bacteria, which fastens the reduction of metal salts to metal NPs. Since fungi are able to grow even in vitro, they have great potential to be used for large-scale NPs synthesis [40]. The most frequently used fungi to produce NPs are *Aspergillus flavus*, *Aspergillus japonicus*, *Candida albicans*, *Candida guilliermondii*, *Cylindrocladium floridanum*, *Geotrichum* sp., *Macrophomina phaseolina*, *Penicillium oxalicum*, *Phanerochaete chrysosporium*, *Rhizopus oryzae*, *Saccharomyces cerevisiae*, and *Trichoderma reesei* (Table 2). Fungi can produce various metals such as Ag, Cu and Au under mild reaction conditions where they act as reducing and stabilizing agents [28]. Many of the proteins secreted by fungi are capable of reducing metal ions

quickly and through non-hazardous processes. In addition, NPs of high monodispersity and dimensions can be obtained from fungi [42].

Filamentous fungi species are more advantageous as they have high metal tolerance and secrete huge quantities of proteins. Hence, they can produce NPs with high stability, which prevents aggregation in NPs even after prolonged storage, and thus have enhanced durability [43]. Besides, fungi are simple to handle and easy to culture on a large scale as they can grow on the surface of an inorganic vector during culture. Filamentous fungi are the right candidate for biomass production for large-scale NPs synthesis compared to algae and bacteria because fungal mycelia are able to withstand flow pressure and agitation in the bioreactors [44].

### 3.3. Green synthesis of metal NPs using algae

Algal organisms such as *Cyanophyceae*, *Chlorophyceae*, *Rhodophyceae*, *Phaeophyceae*, *Sargassum muticum*, *Chaetomorpha linum*, and *Tetraselmis kochinensis* have been used for synthesis of metal NPs such as Au, Ag, and Pd of different sizes and shapes (Table 3). Both live and dead biomasses of algae are utilized for the green synthesis of NPs [45]. The advantages of using algae to produce NPs are high capacity and energy efficiency at low temperature for metal accumulation, reduced toxicity, and easy culturing. Moreover, it is also less harmful to the environment and human in comparison to fungi and

Table 2  
Various metal NPs of different sizes and shapes synthesized from fungi

Species	Nanoparticles	Size (nm)	Morphology	References
<i>Penicillium oxalicum</i>	Ag	4	Spherical	[77]
<i>Aspergillus japonicus</i>	Au	15–20	Spherical	[78]
<i>Stereum hirsutum</i>	Cu and CuO	5–20	Spherical	[79]
<i>Penicillium</i> sp.	Ag	25–30	Spherical	[80]
<i>Macrophomina phaseolina</i>	Ag	5–40	Spherical	[44]
<i>Candida albicans</i>	Au	5–30	Spherical	[81]
<i>Cylindrocladium floridanum</i>	Au	19.05	Spherical	[82]
<i>Rhizopus oryzae</i>	Au	5–65	Spherical	[83]
<i>Saccharomyces cerevisiae</i>	Au	15–20	Spherical	[84]
<i>Phanerochaete chrysosporium</i>	Au	10–100	Spherical	[85]
<i>Penicillium</i> sp.	Au	30–50	Spherical	[86]
<i>Penicillium brevicompactum</i>	Au	25–60	Triangular and hexagonal	[87]
<i>Neurospora crassa</i>	Ag	11–32	Spherical	[43]
<i>Epicoccum nigrum</i>	Au	5–50	Spherical and rod	[88]
<i>Cylindrocladium floridanum</i>	Au	5–35	Spherical	[89]
<i>Trichoderma reesei</i>	Ag	5–50	Spherical	[39]
<i>Geotrichum</i> sp.	Ag	30–50	NR	[42]
<i>Aspergillus flavus</i>	Ag	10–35	Spherical	[90]
<i>Candida guilliermondii</i>	Au	50–70	Spherical	[91]
<i>Pestalotia</i> sp.	Ag	10–40	Spherical	[92]
<i>Rhodospiridium diobovatum</i>	PbS	2–5	Spherical	[93]

Table 3  
Various metal NPs of different sizes and shapes synthesized from algae

Algae	Nanoparticles	Size (nm)	Shape	References
<i>Botryococcus braunii</i>	Ag	40–100	Cubical, spherical, and truncated triangular	[45]
	Cu	10–70	Cubical and spherical	
<i>Gelidium amansii</i>	Ag	27–54	Spherical	[94]
<i>Cystoseira baccata</i>	Au	8.4 ± 2.2	Spherical	[95]
<i>Caulerpa racemosa</i>	Ag	25	Distorted spherical	[47]
<i>Caulerpa serrulata</i>	Ag	10 ± 2	Spherical and ellipsoidal shapes beside	[96]
			Minor amounts of silver nanocubic and nanorods	
<i>Turbinaria conoides</i>	Au	12–57	Spherical	[97]
<i>Sargassum tenerrimum</i>		5–45		
<i>Caulerpa racemosa</i>	Ag	5–25	Spherical with few triangular	[98]
<i>Chlorella vulgaris</i>	Au	10–12	Spherical	[48]
<i>Sargassum</i>	Pd	5–10	Octahedral	[99]
<i>Spirulina platensis</i>	Au	2–8	Spherical	[100]
<i>Bifurcaria bifurcata</i>	CuO	5–45	Spherical	[101]
<i>Sargassum muticum</i>	Au	5.42 ± 1.18	Spherical	[102]
<i>Cystophora moniliformis</i>	Ag	–	Spherical	[103]
<i>Prasiola crispa</i>	Au	5–25	Spherical	[104]
<i>Scenedesmus</i> sp.	Ag	5–10	Spherical	[105]
<i>Spirogyra varians</i>	Ag	35	Quasi-spherical	[106]
<i>Sargassum muticum</i>	Fe <sub>2</sub> O <sub>3</sub>	18 ± 4	Cubic	[107]
<i>Chaetomorpha linum</i>	Ag	3–44	NR	[108]
<i>Tetraselmis kochinensis</i>	Au	5–35	Spherical and triangular	[109]
<i>Chlorella pyrenoidosa</i>	Au	25–30	Spherical	[110]
<i>Spirulina platensis</i>	Ag, Au	7–16 (Ag), 6–10 (Au)	Spherical	[49]
	bimetallic	and 17–25, (bimetallic)		

bacteria, which makes them a potential biological factory for the synthesis of NPs [23]. Algae have a great ability in metal uptake which makes them cost-effective and eco-friendly. They possess secondary metabolites such as tannins, polysaccharide, steroids, and proteins as bioactive compounds. These bioactive compounds are formed when the algal cells convert solar energy to chemical energy during photosynthesis [46]. They have phytochemicals such as ceramides, sesquiterpenes and alkaloids caulerpin. They also contain reducing sugars such as glucose, mannose, galactose, xylose, rhamnose and arabinose and amino acids such as phenylalanine, leucine, serine, glycine, aspartic acid, glutamic acid, isoleucine, valine, lysine and alanine. The presence of reducing sugars gives them the ability to easily reduce metal ions to metal [47], while phytochemicals in algae such as amino functional groups, hydroxyl, alkaloids, and carboxyl act as effective reducing and capping agents to prevent aggregation of metal NPs to produce NPs of high stability [48]. The carboxyl groups in algae can bind to various metal ions, while intracellular polyphosphates and extracellular polysaccharides of live algae can contribute in metal separation [49]. Seaweeds have also been explored for NPs synthesis as they are a good source of phenolic compounds, amino acids, alkanes, terpenoids, ketones, phlorotannins, cyclic polysulfides and steroids [50]. All these bioactive compounds and phytochemicals produce better NPs that exhibit biological

activities such as anti-inflammatory, antibiotic, antimitotic, antiviral, antifouling, and antineoplastic [51]. In brief, using algae in synthesis of NPs is advantageous because they demand none or less utilization of harsh chemicals and are naturally renewable, recyclable, and easily available all year round. In addition, their preparation steps are minimal. Moreover, they show outstanding retention capacity and have various multifunctional groups on their surface.

#### 3.4. Green synthesis of metal NPs using plant extracts

While microorganisms such as bacteria, fungi, and algae are being explored in synthesis of metal NPs, the use of parts of whole plant for generation of NPs have also been extensively investigated in recent years as there is no need to maintain cell culture [52]. This lessens the expenses for preparation of culture media and microorganism and does not pose a biohazard problem [4,6]. The capability of plant extracts to reduce metal ions has been known since the early 1900s. However, it is only over the past few years that the use of plant extracts and plant tissues for reducing metal ions to NPs has attracted considerable attention. The use of plant extracts is known for its sustainability, eco-friendliness, diversity, and non-pathogenicity. Plant extracts are also a renewable source and reliable for synthesis of various NPs [38,39]. Plant-mediated synthesis of NPs

is based on the capability of the plant's system to uptake, accumulate, utilize, and recycle various mineral species and degrade inorganic metallic and metallic oxide ions from their environment [53]. Plants such as *Abelmoschus esculentus*, *Thymus vulgaris*, *Melissa officinalis*, *Pithecellobium dulce*, *Tecoma castanifolia*, *Atalantia monophylla*, *Aegle marmelos*, *Tabernaemontana divaricata*, *Artocarpus gomezianus*, and *Prosopis farcta* have been used to synthesize metal NPs such as ZnO and CuO of different sizes and shapes (Table 4). The advantages of plant-mediated biosynthesis compared to microbes are that it eliminates the complex maintenance of cell cultures, is safe to handle, requires only a one-step simple process, is easily available, and is cost-effective. Moreover, plants contain numerous metabolites that are responsible for the reduction of metal ions and stabilize NPs to produce NPs of controlled size and shape, which

are suitable for large-scale production [21]. The growth of particle size can be controlled by manipulating synthesis conditions like pH, temperature, mixing ratio of the reactants, and concentration of reducing agent [1].

Phytochemicals in plants such as ketones, saponins, aldehydes, flavones, amides, terpenoids, carboxylic acids, phenols, polysaccharides, reducing sugars, quinones, organic acids and ascorbic acids act as both reducing and stabilizing agents in the synthesis of NPs. Hence, they are considered as the best sources to make natural NPs with preferred shapes and sizes [54]. NPs can be synthesized by using extracts of plant leaves, seeds, fruits, fruit peels, flowers, and barks as reducing and capping agents (Fig. 4) [55]. Previous studies have proved that highly stabilized NPs are produced from plant extracts compared to those from microbe-based synthesis [5,31]. Compared with microbial

Table 4  
Various metal NPs of different sizes and shapes synthesized from plant extracts

Plants	Nanoparticles	Size (nm)	Plant's part	Shape	References
<i>Abelmoschus esculentus</i>	ZnO	29	Mucilage	Spheres and elongated and rodlike structures	[111]
<i>Thymus vulgaris</i>	ZnO	50–60	Leaves	Irregular (mostly spherical)	[53]
<i>Melissa officinalis</i>	CuO/ZnO	10–20	Leaves	Spherical	[112]
<i>Pithecellobium dulce</i>	ZnO	30	Peel	Spherical	[113]
<i>Tecoma castanifolia</i>	ZnO	70–75	Leaves	Spherical	[114]
<i>Atalantia monophylla</i>	ZnO	30	Leaves	Spherical and hexagonal	[115])
<i>Aegle marmelos</i>	NiO	8–10	Leaves	Spherical	[116]
<i>Tabernaemontana divaricata</i>	ZnO	20–50	Leaves	Spherical	[117]
<i>Artocarpus gomezianus</i>	ZnO	31–40	Fruit	Spherical	[118]
<i>Prosopis farcta</i>	Ag	16	Seed	Spherical	[119]
	ZnO	26			
<i>Moringa oleifera</i>	ZnO	13–61	Leaves	Leaves	[120]
<i>Vitis labrusca</i>	ZnO	20	Fruit Skin	Hexagonal hollow pyramids	[121]
<i>Coriandrum sativum</i>	Fe <sub>2</sub> O <sub>3</sub>	20–90	Leaves	Spherical	[122]
<i>Passiflora caerulea</i>	ZnO	70	Leaves	Spherical	[123]
<i>Artocarpus heterophyllus</i> L.	ZnO	10–15	Leaves	Spherical	[124]
<i>Carica papaya</i>	ZnO	50	Leaves	Spherical	[125]
<i>Abutilon indicum</i>	CuO	16.78	Leaves	Spherical	[126]
<i>Citrus aurantifolia</i>	ZnO	50	Fruit peel	Pyramid	[58]
<i>Lycopersicon esculentum</i> (tomato), <i>Citrus sinensis</i> (orange), <i>Citrus paradisi</i> (grapefruit), <i>Citrus aurantifolia</i> (lemon)	ZnO	9.7 ± 3	Fruit peel	Polyhedral	[127]
<i>Citrus maxima</i>	ZnO	10–20	Fruit	Spherical	[128]
<i>Lycopersicon esculentum</i>	ZnO	7–20	Leaves	Hexagonal	[129]
<i>Ceropegia candelabrum</i>	ZnO	12–35	Leaves	Hexagonal	[130]
<i>Acalypha indica</i>	ZnO	20–107	Leaves	Rod	[131]
<i>Lagerstroemia speciosa</i>	Au	41–91	Leaves	Triangular and hexagonal with a minor presence of spherical	[132]
<i>Carissa edulis</i>	ZnO	50–55	Fruit	Flower-shaped	[133]
<i>Laurus nobilis</i>	ZnO	47.27	Leaves	Flowerlike and hexagonal	[134]
<i>Nyctanthes arbor-tristis</i>	ZnO	12–32	Flower	Spherical	[3]



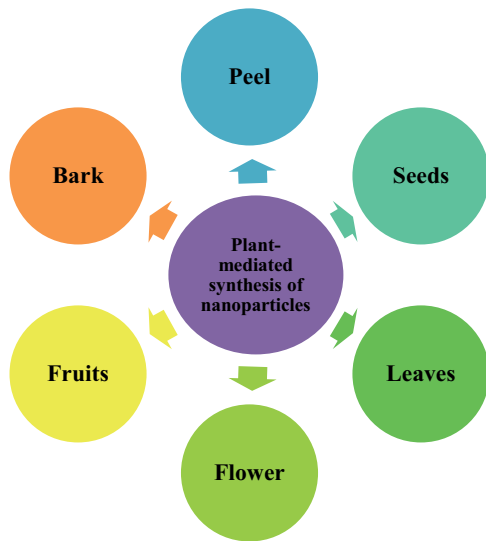


Fig. 4. Parts of plants used for the synthesis of NPs.

systems, plant-mediated synthesis of NPs requires shorter incubation period and can be scaled up easily for commercial needs [56]. The plant extract is mixed with metal salt solution at room temperature and the complete reaction occurs in a few minutes [57]. The schematic representation of synthesis of metal NPs using plant extract is shown in Fig. 5 and the possible mechanism for the formation of ZnO NPs is illustrated in Fig. 6 [58].

**4. Application of green-synthesized NPs in various fields**

Green-synthesized metal NPs have been explored in different fields such as medicine and agriculture because they are nontoxic and environmentally benign. Nanotechnology has become a sensation in the medical field, especially in the identification of cancer. For example, green-synthesized Ag NPs from *Punica granatum* leaves has anticancer potential against human liver cancer cells (HepG2) [59]. Moreover, Ag NPs synthesized using *Gelidiella* sp. extract have been evaluated for their in vitro anticancer activity against human epidermoid larynx carcinoma cell line and their cytotoxicity to the cell line increased as the concentration of the Ag NPs increased [60]. Generally, biosynthesized NPs

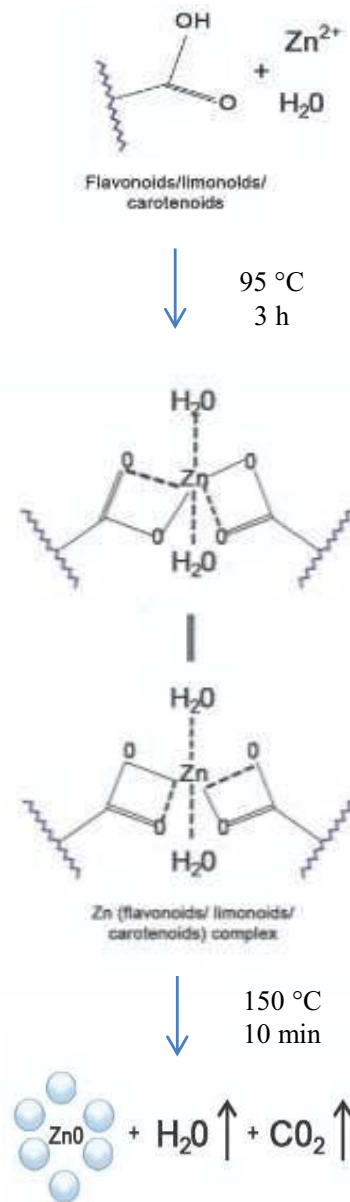


Fig. 6. Possible mechanism for the formation of ZnO NPs (adapted from [58]).

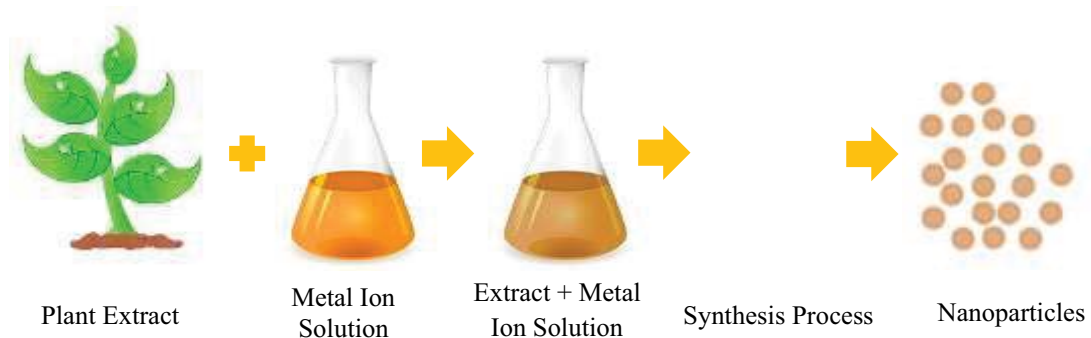


Fig. 5. Synthesis of metal NPs using plant extract.

such as Au, Ag, Cu, ZnO and Pd are used as biosensors, in crop protection, and to improve the productivity of crops due to their antimicrobial characteristics. For instance, Ag NPs synthesized from pine cone extract showed antibacterial property which can be effectually used against agricultural pathogens [61]. Besides that, biosynthesized Au NPs are a significant device for hormone (HCG) detection in urine samples of pregnant women [62]. Moreover, some studies also reported enzyme-based NP biosensors using Ti, AuPt, and lead dioxide (PbO<sub>2</sub>) NPs to detect the presence of some residues of organochlorines, carbamates, and organophosphates [63]. The possible hypoglycemic effects of Ag NPs produced using plant resources have also been evaluated by *in vitro*  $\alpha$ -amylase and  $\alpha$ -glycosidase inhibition assays [64]. Similarly, a study reported antidiabetic activity in a dose-response inhibitory manner on  $\alpha$ -amylase enzyme by Ag NPs synthesized using *Sphaeranthus amaranthoides* extract [65]. Recently, AuNPs synthesized using Panax ginseng berry extract showed enhanced moisture retention in cosmetic products such as anti-aging cream, skin wound disinfection, and face pack cream [66].

## 5. Conclusions

Due to the environmental hazards that arise from physical and chemical syntheses of metal NPs, research has centralized on synthesizing NPs by using biological sources. This green nanotechnology innovation has been established to be the most auspicious and environmentally friendly method for NPs synthesis. This route is eco-friendly, non-toxic, and more applicable for biomedical and agricultural applications. Further development and exploration in green nanotechnology field will definitely develop our knowledge to enhance our understanding in green synthesis of NPs, which will help in applications of NPs in various fields.

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