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A review on medicinal and potential applications of green synthesis: Mediated metal nanoparticles

Sarvaree Bano
Department of Chemistry, Kalinga University, Naya Raipur, Chhattisgarh, India
Email: Sarvaree.bano@kalingauniversity.ac.in

Abstract---The past decade has witnessed a phenomenal rise in nanotechnology research due to its broad range of applications in diverse fields including food safety, transportation, sustainable energy, environmental science, catalysis, and medicine. The distinctive properties of nanomaterial's (nano-sized particles in the range of 1 to 100 nm) make them uniquely suitable for such wide range of functions. The nanoparticles when manufactured using green synthesis methods are especially desirable being devoid of harsh operating conditions (high temperature and pressure), hazardous chemicals, or addition of external stabilizing or capping agents. Numerous plants and microorgan- isms are being experimented upon for an eco–friendly, cost–effective, and biologically safe process optimization. This review provides a comprehensive overview on the green synthesis of metallic NPs using plants and microorganisms, factors affecting the synthesis, and characterization of synthesized NPs. The potential applications of metal NPs in various sectors have also been highlighted along with the major challenges involved with respect to toxicity and translational research.

Keywords---green synthesis, metal nanoparticles, wastewater treatment, agriculture, food application.

Introduction

During the last two decades, nanotechnology has taken massive leaps to become one of the most researched and booming fields due to its applications in various fields of human welfare. Nanoparticles (NPs) are naturally occurring or engineered extremely small sized particles in the range of 1 to 100 nm. They exhibit unique and valuable physical and chemical properties. At nanoscale, particles display better catalytic, magnetic, electrical, mechanical, optical, chemical, and biological properties. Due to high

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surface to volume ratio, NPs show higher reactivity, mobility, dissolution properties, and strength [1]. NPs are thought to have been present on earth since its origin in the form of soil, water, volcanic dust, and minerals. Besides their natural origin, humans have also started synthesizing NPs through various methods [2]. NPs and their derived nanomaterials are finding wide application in various sectors such as food, agriculture, cosmetics, medicines, etc. Applica- tion of NPs in food sector involves food processing and preservation (nanopreservatives, toxin detection, nanoencapsulated food additives, etc.) and food packaging (nanocoatings, nanosensors, nanocomposites, edible coating NPs, etc.)

In agriculture, nanotechnology is being utilized for the production of nano- fertilizers, pesticides, herbicides, and sensors. In medicine, nanotechnology involves production of various antibacterial, antifungal, antiplasmodial, anti–inflammatory, anticancer, antiviral, antidiabetic, and antioxidant agents. Nanotechnology is also useful for the early detection of life-threatening diseases such as cancer. Besides, NPs have also been used for bioremediation due to their capacity to degrade various pollutants such as organic dyes and chemicals. Given the diverse scope of nanomaterials, different countries are investing in nanotechnology with USA and China emerging at the top. In 2019, the global market of different nano products was more than8 billion US dollars, which is expected to show annual growth rate of around 13% by 2027. Depending on their chemical composition, four major classes of NPs are described, such as carbon-based (nanotubes and nanofibers of carbon, etc.), metal and metal ox- ide based (Ag, Cu, etc.), bio-organic based (liposomes, micelles, etc.), and composite based [3]. NPs can also be classified as organic and inorganic in nature [4]. Organic NPs are biodegradable in nature and include polymeric NPs, lip id based nanocarriers, lipo- somes, carbon-based nanomaterials, and solid lipid NPs, while inorganic NPs are based on inorganic materials comprising of metals and metal oxides such as silver oxide, zinc oxide, etc. Among all the synthesized NPs, silver NPs (Ag NPs) are the most widely employed, showing their dominance in various consumer products (more than 25%) [5]. AgNPs are majorly used as antibacterial, antifungal, and antiviral agents. With each passing year, novel varieties of NPs are being developed using state-of-art technology having diverse applications in various sectors.

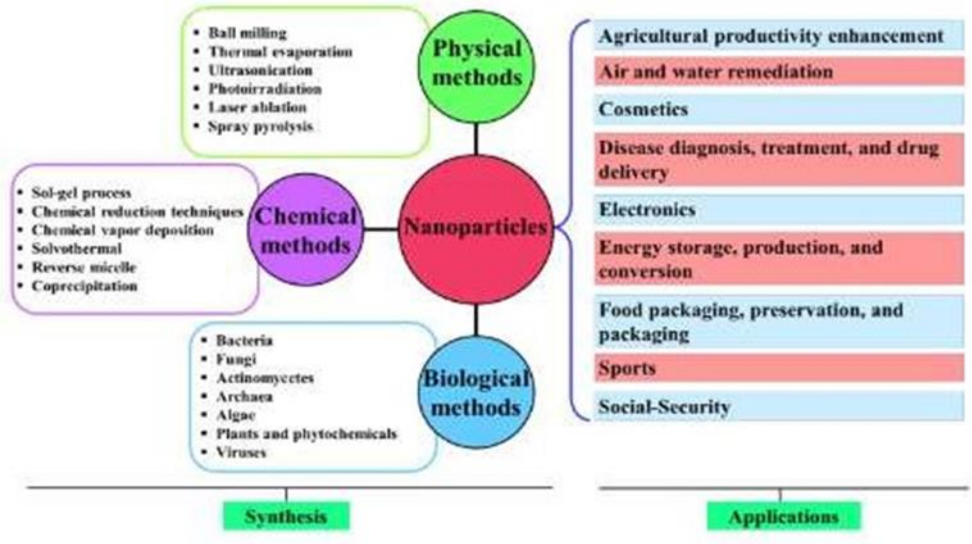

Figure 1. Schematic representation of various methods adopted for NP synthesis and its applications

The synthesis of NPs can be carried out following two different approaches, viz., (i) top-down approach, and (ii) bottom-up approach [6,7]. Furthermore, three different strategies such as physical, chemical, and biological methods are adopted for the synthesis of NPs. A schematic representation of various methods adopted for NPs synthesis and its applications is depicted in Figure. The physical methods belong to the category of top-down approach, while the chemical and biological methods follow the bottom-up approach for the synthesis NPs. Evaporation-condensation, electrolysis, diffusion, laser ablation, sputter deposition, pyrolysis, plasma arcing, and high energy ball milling are some of the most common physical methods used for the synthesis of NPs [8]. However, low production rate, expensive opera- tions, and high energy consumption are the major limitations of these processes. Conversely, chemical synthesis methods that include chemical reduction, micro-emulsion/colloidal, electrochemical, and thermal decomposition are the conventional and most widely used methods for the synthesis of metallic NPs. The chemical reduction of NPs from their respec- tive metal salt precursors by adding particular reducing agents is one of the most widely used methods for NPs chemical synthesis due to easy operational and equipment require- ment. Several reducing agents, such as sodium borohydride (NaBH4) [9], potassium bitar- trate [10], formaldehyde [11], methoxypolyethylene glycol [12], hydrazine [13], etc., and stabilizing agents like dodecyl benzyl sulfate [14] and polyvinyl pyrrolidone [15] have been explored during synthesis. The chemical methods are economical for large-scale production; however, the use of toxic chemicals and production of harmful by-products cause environ- mental damage, thereby limiting its clinical and biomedical applications [16,17]. Hence, there is an increased demand for reliable, nontoxic, high- yielding, and eco-sustainable techniques for metallic NPs that can replace the conventional methods. The biological synthesis methods, therefore, provide an attractive alternative to the physicochemical synthesis methods. The present article provides a critical overview on the synthesis of metallic NPs using biological methods and several factors affecting the preparation process. The applications of NPs in various sectors, such as medicine, wastewater treatment, agricultural sectors, etc., have been discussed in detail. Current challenges highlighting the toxic effects of NPs and future perspectives in each section gives us a comprehensive way forward in the near future.

Biological synthesis of NPS

The biological synthesis of NPs can be carried out using a vast array of resources such as plants and plant products, algae, fungi, yeast, bacteria, and viruses. The synthesis of NPs is initiated by the mixing of noble metal salt precursors with biomaterials [18]. The presence of various compounds, such as proteins, alkaloids, flavonoids, reducing sugars, polyphenols, etc., in the biomaterials act as reducing and capping agents for the synthesis of NPs from its metal salt precursors [19]. The reduction of metal salt precursor to its successive NPs can be initially confirmed by visualizing the color change of the colloidal solution. Several studies reported the synthesis of Ag, Au, Cu, Pt, Cd, Pt, Pd, Ru, Rh, etc. using various biological agents in the recent past.

Plant-Mediated Synthesis of NPs

Figure shows the Scopus search (with keywords “metal nanoparticles” and “plant extract”) results of the number of research published from last 10 years on biological synthesis of NPs. An increase in the number of research publications was observed with each year and approximately 468 publications reported in the year 2020. These data further corroborate that the research interest in the area of biological NPs using plant extract is increasing significantly every year.

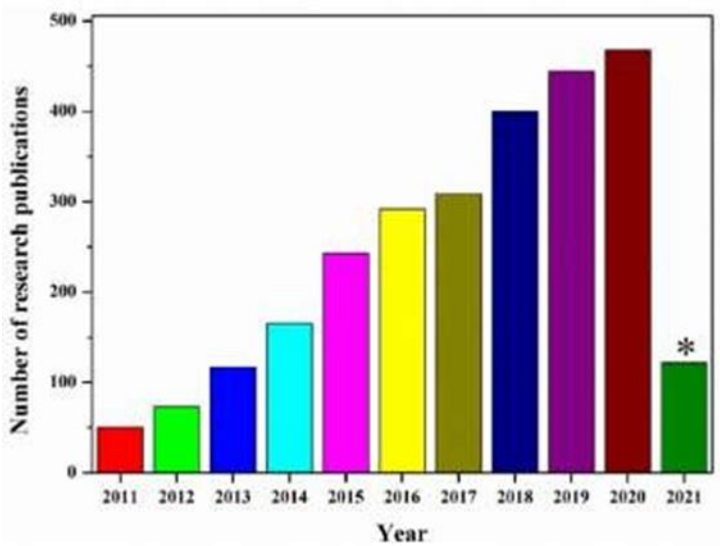

Figure 2. Number of research publications on biological synthesis of metallic NPs from last 10 years

Synthesis of a wide range of metallic NPs has been reported using various plants. Plant mediated synthesis of NPs can be achieved by three different methods, viz., (i) in- tracellularly (inside the plant), (ii) extracellularly (using plant extracts), and (iii) using individual phytochemicals. Several plants have the capability of metal accumulation and successive conversion of these accumulated metals to NPs intracellularly. The presence of several biomolecules such as amino acids, alkaloids, aldehydes, flavones, ketones, proteins, phenolics, polysaccharides, saponins, tannins, terpenoids, and vitamins in the plant plays a key role in the reduction of metals. The variation in the size, shape, and properties of accumulated NPs are observed due to the variation in stabilizing and reducing potential of biomolecules present in the plant. The formation of gold NPs inside the living plant, alfalfa was reported by Gardea-Torresdey et al. when the plants were grown in AuCl4 rich environment. In a similar kind of study, Bali and Harris observed the ability of Medicago sativa and Brassica juncea plants to accumulate Au NPs from aqueous solutions of KAuCl4. The NPs were majorly located in the xylem parenchyma cells while some were also accumulated throughout the epidermis, cortex, and vascular tissue.

Microbial Synthesis of NPs

In addition to the plant- mediated synthesis, several microorganisms such as bacteria, fungi, actinomycetes, and viruses are also reported to synthesize various metal NPs. The interaction between metals and microorganisms have been exploited in the past for various biological applications such as biomineralization, b ioremediation, bioleaching, and biocorrosion. However, recently microbial synthesis of NPs has emerged as a promising field of research due to certain advantages compared to other methods. The NPs are synthesized either intracellularly or extracellularly depending on the type of microorganisms.

Factors Affecting NPs Synthesis

Adjustment of shape and size of metal NPs further enhances their functionality for various applications. The morphological parameters of NPs can be manipulated by changing various experimental parameters such as reaction time, reactant concentration, pH, temperature, aeration, salt concentration, etc. Precise control of these parameters can play a critical role during the optimization of metal NPs synthesis via the biological route. The size and shape of NPs can be controlled by varying the pH of the medium, while the acid pH leads to the formation of large-sized NPs. During synthesis of Au NPs using oat (Avena sativa) biomass, Armendariz et al. observed smaller sized gold NPs at pH 3.0 and 4.0 in comparison to the synthesized NPs at pH 2.0. This is due to the better accessibility of functional groups present in the extract for nucleation at higher pH compared to the presence of fewer groups at a lower pH range. In addition to pH, t he concentration of biomolecules in the extract also affects the size and shape of synthesized NPs. Increase in the concentrations of Aloe vera leaf extract resulted in the synthesis of higher amount of spherical gold NPs instead of triangular which is due to the presence of carbonyl compounds in the extract. In addition, the size of the NPs was modulated in the range of 50 to 350 nm by varying the extract concentration in the solution.

Characterization of NPs

NPs have attracted significant attention of researchers due to their unique physical, chemical, and mechanical properties. Therefore, the physicochemical characterization of synthesized NPs is critically important before its application in various sectors. Analyzing various characteristics such as size, shape, surface morphology, surface area, structure, stability, elemental and mineral decomposition, homogeneity, intensity, etc. will provide important information about the NPs, which subsequently determined their end- use ap- plications. Additionally, the electrical and thermal conductivity and purity of NPs can also be obtained by using these techniques. Size and shape of the synthesized NPs are mainly analyzed using X-Ray Diffraction (XRD), Scanning Electron Microscope (SEM), Field Emission Scattering Electron Microscopy (FESEM), Transmission Electron Microscopy (TEM), High-Resolution Transmission Electron Microscopy (HRTEM), Atomic Force Mi- croscopy (AFM), Dynamic Light Scattering (DLS), Condensation Particle Counter (CPC), Photon Correlation Spectroscopy (PCS), etc. Among these techniques, XRD, SEM, and TEM are most commonly used for this purpose. Further, SEM, TEM, AFM, etc. are used for studying the surface morphology. Superconducting Quantum Interference Device (SQUID), Vibrating Sample Magnetometer (VSM), Electron paramagnetic resonance (EPR), etc. are used for the determination of magnetic properties of NPs.

Potential applications of metal NPS

These synthesized metallic NPs offer a diverse platform for various applications. Some of the most important applications of these metallic NPs are summarized in this section.

- **Agriculture**- Nanotechnology has proven its potential to benefit the agriculture sector by finding solutions to agricultural and environmental problems in order to increase food production and security.
- **Nanoparticles in Food Industry-** NPs in combination with other technologies can bring impactful innovations in the production, storage, packaging and transportation of food products.
  Food processing transforms raw food ingredients into a palatable format with long shelf- life and in turn, ensure efficient marketing and distribution systems for the enterprise. Fresh foods, on the other hand, require robust logistics for their transportation from source to consumer. Nan- otechnology based systems play an important role to maintain the functional properties by incorporating NP based colloids, emulsions, and biopolymers solutions. Nanotechnology has provided with a new dimension and ample opportunities to develop NPs for various applications with deeper knowledge of the material. Application of nanotechnology in food industry is based on nanostructures which target food ingredients as well as sensors. Nano-food ingredients cover a wide area of applications starting from processing of food to its packaging. Nanostructure based application in food processing comprises the use as antimicrobial agents, nanoadditives, nanocarriers, anticaking agents, and nanocomposites while in food packaging, they are applied as nano-sensors for monitoring

the quality of food produced. The nano materials can also serve as enzyme-supports because of their large surface-to-volume ratio with respect to their conventional macro-sized counter- parts.

- **Drug and Medicine-** Nanotechnology-based drugs have attracted a lot of attention in the last decade. The unique properties of NPs, viz., small size, ability to travel through fine blood capillaries, vessels, junctions, and barriers, have made them one of the most researched and studied domains. They have great advantages in terms of improvement of bioavailability of drugs, solubility, toxicity safeguard, pharmacological activities, distribution, and pre- vention from chemical and physical degradation and increased stability of drugs inside the body. Nanomedicines have shown higher capacity to bind with biomolecules as well as reduction of inflammation/oxidative stress in tissues. Thousands of different nanomedicines have been designed over the years; they have various applications in differ- ent types of diseases. Few are approved for clinical use, and many more are in the phase of clinical trials.
- **Wastewater Treatment Process-** The increase in population growth rate, industrialization, and excessive use of chemicals has contaminated the aquatic environment b y releasing wastewater to the environment. The water from natural resources is not suitable for consumption due to the presence of organic (dyes, pesticides, surfactants, etc.), inorganic (fluoride, arsenic, copper, mercury, etc.), biological (algae, bacteria, viruses, etc.), and radiological contaminants (cesium, plutonium, uranium, etc.). Figure depicts some of the common contaminants found in water. Several techniques such as physical, chemical, and biological have been adopted for the treatment of wastewater. However, search for new efficient technologies to improve water purification at low-cost is the current research focus. Several approaches have been developed in combination with various NPs for the successful removal of contaminants from wastewater as shown in Figure.

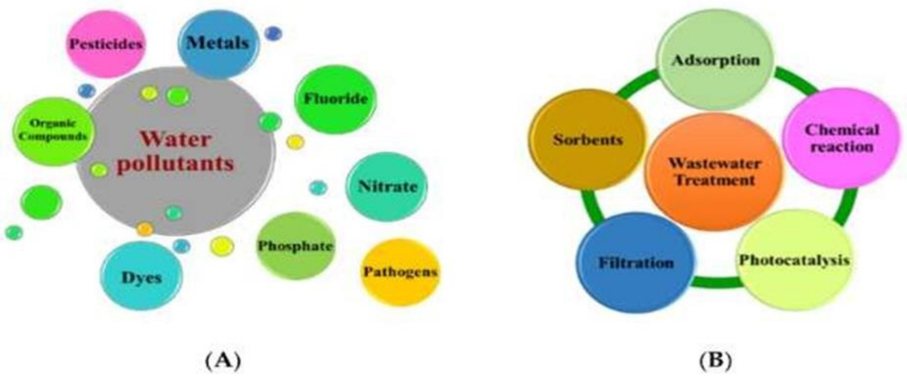

Figure 3. Common pollutants found in water and the treatment processes. (A) Common pollutants present in water. (B) Treatment approaches used for wastewater using nanoparticles

Antimicrobial Activity

In the past decade, application of nanomaterials to control microbial proliferation has garnered much interest from scientists worldwide. The increase in resistance of microorganisms to antimicrobial agents, including antibiotics, has led to a spike in health related complications. A vast body of work has revealed that by combining three forces of material science, nanotechnology, and the inherent antimicrobial activity possessed by certain metals, innovative applications for metal NPs can be identified. Previous studies have reported that metal and their counterpart metal oxide nanoparticles have displayed toxicity towards numerous microorganisms. These NPs may be used successfully to stop the growth of various bacterial species.

Toxicity of metal nanoparticles

NPs have wide applicability in different sectors such as electronics, agriculture, chem- icals, pharmaceutical, food, etc. due to their unique physicochemical properties. The most commonly used NPs by various sectors include metal oxide NPs such as silicon oxide (SiO2), titanium dioxide (TiO2), zinc oxide (ZnO), aluminum hydroxide [Al(OH)3], cerium oxide (CeO), copper oxide (CuO), silver (Ag), nanoclays, carbon nan- otubes, nanocellulose, etc. However, massive release of NPs into the environment (air, water, and soil) by various industries is resulting in production of nanowaste and proving to be dangerous for the living organisms and causing threat to ecosystem balance. Various characteristics of NPs affecting their toxicity are size, nature, reactivity, mobility, stability, surface chemistry, aggregation, storage time, etc. NPs cause adverse consequences on human health and animals. Use of NPs has intensified the risk of various diseases in humans such as diabetes, cancer, bronchial asthma, allergies, inflammation, etc.[3]. The animal reproductive system has also been shown to be affected due to toxicity of various NPs such as Au, TiO2, etc. NPs enter the animal body through ingestion and inhalation and get absorbed by the cells through the processes of phagocytosis and endocy- tosis and induce the generation of reactive oxygen species (ROS), ultimately resulting into lipid peroxidation, mitochondrial damage, etc. Different NPs such as Ag, Cu, ZnO, Ni, etc. have also reduced the enzymatic activity of various microorganisms. In addition, excessive production of NPs is also affecting the food web of the ecosystem. Toxicity effects of NPs over plants, animals, and microorganisms are shown in Figure.

Impact of Nanoparticle Toxicity on Plants

Plants are of high fundamental significance as they perform photosynthesis and release oxygen in the atmosphere. As all the plant parts (roots, shoots, and leaves) are in direct contact with environmental matrices (air, water, and soil), they may get affected more by the NPs contamination as compared to the other living beings. NPs present in the atmosphere can enter into the plant body through the stomatal openings on leaves, while those present in soil and water can be selectively up taken by the plant roots. NPs proved to be toxic to plants and hamper their growth and development. The toxicity in plants is mainly due to ROS production, causing lipid peroxidation and ulti- mately leading to DNA damage, reduction in photosynthetic pigments, plant biomass, soluble protein content reduction, etc. However, plants have a defensive system against oxidative stress in the form of enzymatic and non-enzymatic antioxidants, which may become inefficient under higher oxygen concentrations.

Toxicity of Nanoparticle-Based Drugs

The commercial applications of NPs as therapeutics for treatment of diseases is a double-edged sword. Even though many studies are being done worldwide to analyze the toxic effects of NM exposure, the possible mechanism of NMs interactions with biological systems and their consequences are still unknown. Research has shown that NPs can travel through the bloodstream and easily cross membrane barriers. This in turn can adversely affect tissues and organs at molecular and cellular levels. NPs have demonstrated the capacity to cross the blood–brain barrier (BBB) and gain access to the brain. Small size, large surface area to mass ratio (SA/MR), and surface characteristics determine nanoparticle's interaction with biological milieu and the resultant toxic effects that ensue.
The unique nature of the NMs allow them to easily pass-through cell and tissue membranes and cellular compartments to cause cellular damage. The large SA/MR of NPs also remains open for active chemical interactions with cellular macromolecules. Increase in surface area of the identical chemical further enhances adsorption properties, surface reactivity, and potential toxicity.

Major challenges and future perspective

In the recent past, research on NPs and their potential applications have progressed by leaps and bounds. Numerous studies have reported the green synthesis of metallic NPs using various biological sources such as plants, bacteria, fungi, and yeast. However, several challenges persist, which limit its large-scale production and consequent applications. Some of the major challenges observed during the synthesis are summarized below:

- Detailed optimization studies on reactants (plant extract, microorganism inoculum,
- fermentation medium composition, etc.) and process parameters (temperature, pH, rotational speed, etc.) are required to control the size and shape of the NPs.
- Studies also need to be focused on enhancing various physicochemical characteristicsof NPs for specific applications.
- The involvement of each metabolite of plant extract and cellular components ofmicroorganism in the synthesis of NPs should be completely analyzed.
- Scale-up of NPs production for commercial purposes using green synthesis methodsneeds to be prioritized.
- Improvement of NPs yield and stability with reduced reaction time is needed byoptimizing various reaction parameters.

Addressing these challenges could make the green synthesis methods cost-effective and comparable to the conventional methods for the large-scale production of NPs. Additionally, the separation and purification of NPs from the reaction mixture is another important aspect that need to be explored. A detailed toxicological study of the NPs on plants and animals is necessary for expanding its application in diverse fields. In addition to wild type strains, genetically modified microorganisms with the ability to produce greater quantity of enzymes, proteins, and biomolecules could further enhance the biosynthesis as well as the stabilization of NPs. Further, enhancement of metal accumulation capacity and tolerance of genetically modified microorganisms could provide a futuristic approach for the production and application of metal NPs using the green synthesis method.

Conclusion

The present review focuses on the green synthesis of metal NPs derived from plants and microorganism and their applications. Green synthesis methods provide a clean, non-toxic, and eco-friendly approach for the synthesis of metal NPs compared to other conventional techniques like physical and chemical methods. A wide range of plant materials including leave extract, fruit extract, seed, fruit, bark, etc. and microorganism such as bacteria, fungi, actinomycetes, etc. have shown potential for synthesis of various metal and metal oxide NPs (viz., Au, Ag, Pt, Pd, Ni, Se, Cu, CuO, and TiO2). The size and shape of NPs and the reaction rate strongly depend on various experimental parameters such as reaction time, reactant concentration, pH, temperature, aeration, salt concentration, etc. Different characterization techniques such as UV-VIS spectroscopy, FTIR, XRD, SEM, TEM, EDX, and AFM have been used to determine the shape, size, and morphology of biosynthesized NPs. However, in terms of translational research, several factors, viz., bioavailability, adverse reactions, cellular interactions, biodistribution, and biodegradation, need to be addressed. The accumulation of these NPs in the environment and their uptake by biological systems can lead to disastrous consequences as a number of studies show evidence of NPs causing DNA and membrane damage, protein misfolding, and mitochondrial damage. Although numerous studies reported the biological synthesis of metal NPs, a thorough investigation is the need of the hour for widening their applications and successful commercialization.

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