frontiers | Frontiers in Nanotechnology

TYPE Mini Review
PUBLISHED 27 January 2025
DOI 10.3389/fnano.2024.1506665

OPEN ACCESS

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RECEIVED 05 October 2024
ACCEPTED 30 December 2024
PUBLISHED 27 January 2025

CITATION
Parab AR, Ramlal A, Gopinath SCB and Subramaniam S (2025) Forging the future of nanotechnology: embracing greener practices for a resilient today and a sustainable tomorrow. *Front. Nanotechnol.* 6:1506665.
doi: 10.3389/fnano.2024.1506665

Forging the future of nanotechnology: embracing greener practices for a resilient today and a sustainable tomorrow

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Various chemical and physical methods have been proposed for the synthesis of nanoparticles (NPs). However, these methods have disadvantages, such as high energy loss and high capital requirements. To overcome these problems, alternative methods for NP synthesis, such as biological or green synthesis, are favoured to overcome these problems. Green synthesis of NPs is environmentally friendly, economical and non-toxic. This review examines the history of green synthesis, focusing on using environmentally friendly methods. The integration of machine learning into NP production and a range of NP applications in healthcare, disease treatment and the environment are also covered.

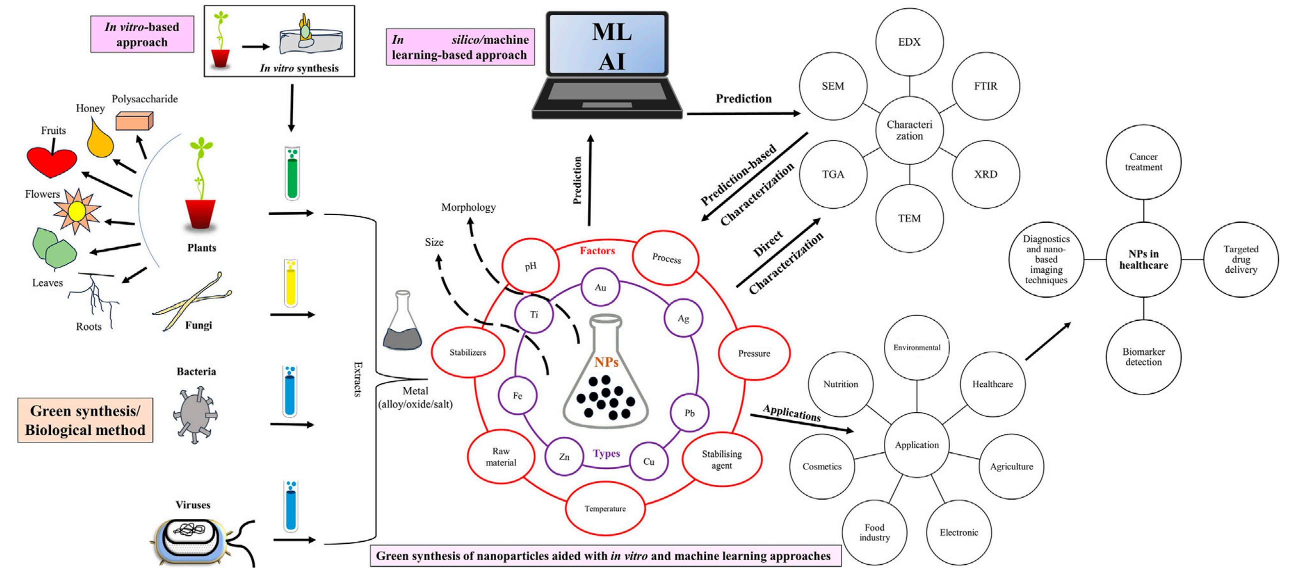
KEYWORDS

green synthesis, nanomaterial, machine learning, sustainable, nanotechnology, healthcare

1 Introduction

One of the foundations of the current nanoscience revolution is the semiconductor nanocrystal as a nanomaterial (Kambhampati, 2021). The size of nanoparticles (NPs) is usually smaller than 100 nm (>1 nm) and due to their smaller size, they are chemically stable (Das, 2017; Marslin et al., 2018). The core of nanobiotechnology is the production of NPs and other nanomaterials, which are used in various industries such as electrochemistry, electrical and mechanical engineering, cosmetology, food, pharmaceuticals, medicine and agriculture (Najahi-Missaoui et al., 2020; Khan et al., 2022). In recent years, the U.S. Food and Drug Administration (U.S. FDA) and the European Medicines Agency (EMA) have approved several pharmaceutical companies for the use and development of nanotechnology-based drugs (Halwani, 2022).

Magnetic NPs derived from iron (Fe) are being actively explored for medical diagnosis and therapy, including cancer treatment (Dürr et al., 2013), sorting and manipulation of stem cells (Barrow et al., 2015), drug delivery (Estelrich et al., 2015), genome analysis (Tang et al., 2020) and magnetic resonance imaging (Zhao et al., 2020), and copper (Cu) NPs are



GRAPHICAL ABSTRACT

used as biosensors and electrochemical sensors (Qing et al., 2019). Many silver (Ag) NPs are commonly used to treat viral and microbial infections (Salleh et al., 2020). Platinum (Pt) NPs have recently been investigated and used for the production of anticancer drugs (Abed et al., 2022).

Nanomaterials are synthesised using two methods, namely, the top-down and the bottom-up approach (Usman et al., 2020). The top-down approach is usually done by physical processes such as vaporisation, lithography, laser ablation, spraying, hydrolysis, photo, irradiation and supersonic. In this method, a larger molecule is broken down into atoms or ions that are much smaller (Gutiérrez-Cruz et al., 2022; Harish et al., 2023). Co-precipitation, photochemistry and reduction are chemical methods that can be used in the bottom-up approach (Wang et al., 2021; Sajid, 2022). The bottom-up method involves using microorganisms plants, algae, bacteria and fungi (Salem and Fouda, 2020; Karunakaran et al., 2023).

This review deals with the green synthesis of nanoparticles through environmentally friendly methods. Different applications of NPs in therapeutics and other fields have also been discussed.

2 Background of green synthesis

Green synthesis (GS) refers to the biological production of NPs using enzymes from microorganisms or phytochemicals or other sources (plants, algae, fungi, etc.) (Jeevanandam et al., 2022; Sharma et al., 2022). GS is a safe, economical, environmentally friendly and clean method of producing nanomaterials. It uses plants and other biological materials such as bacteria, fungi and algae as substrates (Huston et al., 2021; Dikshit et al., 2021). Many variables can affect the nature and size of NPs, depending on the method and component used for production, including temperature, particle size, pH, extract concentration, reaction time, solvent used and surface charge (Lombardo et al., 2020; Shafey, 2020; Usman et al., 2020). Another important parameter for characterising NPs is the type and intensity of the surface charge, which influences the electrostatic interactions between NPs and their environment (Modena et al., 2019). The final shape and size of NPs are determined by various active molecules and precursors, including a metal salt (Dikshit et al., 2021). Phytochemicals (amides, terpenoids, carboxylic acid, ascorbic acid, etc.) can convert metal salts into metal NPs. These potent phytochemicals present in the extracts are the focus of extensive biodiversity research for green production of NPs (Md Ishak et al., 2019).

3 Production of nanoparticles

3.1 Microbial synthesis

Various microorganisms - from bacteria, fungi and actinomycetes to viruses - have been tested for their suitability for the synthesis of NPs. They are used for biocorrosion, bioremediation, biomineralization, bioleaching and other applications in different industries (Dikshit et al., 2021). Microbial synthesis is favoured due to the numerous advantages it offers. They also have advantages such as scaling up the process and other processes associated with synthesis (bottom-up or top-down approaches) (Dikshit et al., 2021) (Supplementary Table 1A).

3.2 Nanoparticles from algal sources

In contrast to plants, algae (microalgae and macroalgae) do not require any special additional chemicals (Mukherjee et al., 2021). The production of NPs using algae is referred to as phyco-nanotechnology (Chaudhary et al., 2020). Algae contain a variety of phytochemicals, proteins and pigments that are ideally suited as bioproducts for the production of NPs. Algae have shorter growth times (high growth rate), are easier to process, less expensive, require fewer nutrients and are non-toxic. The production of NPs in the solution containing algal extract and metal solution is indicated by the change in colour. The colour change indicates that the metal ions are in a zero-valent state. In the production of gold (Au) NPs with *Ulva intestinalis* and *Rhizoclonium fontinales*, there was a visible colour change from green to purple in the thallus (Chaudhary et al., 2020). Similarly, the colour of the cultured mixture of algal biomass of *Clavulina humicola* together with Ag nitrate salts changed to yellow, indicating the formation of AgNPs (Chan et al., 2022). Many other algal species such as *C. humicola, Padina boergesenii, Gracilaria corticate, Anabaena doliolum* and *Spirulina* were used to produce NPs (Supplementary Table 1B).

3.3 Virus-derived nanoparticles

Plant viruses are preferred for the GS of NPs to minimise the risk of the virus interacting with human proteins and causing toxic side effects, infections and immune responses (van Kan-Davelaar et al., 2014). Plant viruses are also ideal because they can self-assemble around a nanoparticle *in vitro* and contain about 10 nm^3 of particles (Alemzadeh et al., 2018; Zhang et al., 2018). These properties are mainly used to produce plant-derived viral NPs that are used for targeted cancer treatment (Zhang et al., 2018; Venkataraman and Hefferon, 2021).

Plant viruses can also be used as size-limiting vessels for the production of NPs. Different sizes of co-particles produce virus-like particles with different properties and distinct symmetries. Particles composed of smaller NP cores are smaller than those composed of large cores (Liu et al., 2021). The process for producing plant viral NPs involves infecting the plant leaf with the plant virus. There are several forms of the viral capsid and it can be divided into different subunits such as the inner, middle interface and outer. This enables numerous applications for a single viral NP (Chung et al., 2020; Steinmetz et al., 2020; Nooraei et al., 2021).

Viral NPs have protein monomers and encapsulate negatively charged nucleic acids. This approach has been used to encapsulate complexes of negatively charged polymers and cytotoxic drugs such as doxorubicin so that the viral NPs can be used for targeted drug delivery systems (Krissanaprasit et al., 2021; Li and Champion, 2022). Encapsulation of these synthetic NPs in viral NPs ensures biocompatibility, prevents aggregation and enables bioconjugation of functional ligands, such as targeting molecules, to achieve tissue specificity (Färkkilä et al., 2021; Tufani et al., 2021). Bio-templating is a process that mimics the process of bio-mineralisation, i.e., the formation of minerals through the metabolic activities of microorganisms (Homaeigohar, 2020; Magdum et al., 2024). *Protein cages for inorganic nanoparticles*: The exterior and interior of the *Cowpea chlorotic mottle virus* capsule are chemically different environments (Kumari et al., 2021). The inner surface is more positively charged than the outer surface so it can serve as a nucleation site for crystal growth. The inner cavity of the virion restricts mineral growth. Therefore, a spherical nanoparticle with a maximum diameter of about 28 nm is formed (Chakravarty and Rao, 2023).

3.4 Plants and their extracts: reducing and stabilizing agents

The simplest green production method for the production of metal and metal oxide NPs is the use of plant extracts (Jeevanandam et al., 2022). Various metabolites or chemical substances can be found in plant extracts. They can act as stabilisers that enable the biodegradation of metal ions to NPs. For example, to produce gold NPs, a metal salt solution such as $HAuCl_4$ and $AgNO_3$ is added to the plant extract, and amino groups ($-NH_3$) help to degrade the metal ions from the salt solution (Bharadwaj et al., 2021). The activation phase, the growth phase and the process completion phase are all involved in the synthesis of NPs with plant extracts. In the activation phase, the reduction of metal ions takes place. As a result, reduced metal atoms are formed, followed by a phase change of the nucleated metal atom to the metal ion. The newly formed metal ion grows and is further reduced in the subsequent growth phase. Plant tissues from *Ocimum sanctum, Desmodium trifolium, Cinnamomum zeylanicum, Piper longum, Syzygium cumini* and *Melia azedarach* have been used to reduce Ag ions to particle sizes of 5–40 nm (Gour and Jain, 2019). According to Yadi et al. (2018), extracts from *Calotropis procera* and *Punica granatum* are mixed with Cu acetate to produce CuONP. The plant extracts can calcify Cu acetate to CuNPs (Supplementary Table 1B).

3.5 *In vitro* synthesis of nanoparticles

The development and synthesis of NPs using *in vitro* approaches is still in its infancy. Only a few reports have demonstrated the use of *in vitro*-based synthesis of NPs (Satyavani et al., 2011; Iyer et al., 2016; Jayappa et al., 2020). Satyavani et al. (2011) and Iyer et al. (2016) synthesised 31 and 1 nm AgNPs from stem-derived calli extracts of *Citrullus colocynthis* (L.) Schrad. (Cucurbitaceae) and calli culture of *Vigna radiata* (L.). R. Wilczek (Fabaceae) using Murashige and Skoog (MS) medium supplemented with different plant growth regulators. Zinc oxide (ZnO) NPs (5–20 nm) were synthesised by Jayappa et al. (2020) using the leaf callus of *Mussaenda frondosa* L. cultured on MS medium with NAA 2 mg/L and kinetin (kin) 4 mg/L. Therefore, the *in vitro* approaches for the synthesis of NPs need to be explored as they could be a potential method for the rapid and efficient generation of NPs.

4 Characterization of nanoparticles

Common techniques used to characterise NPs are surface-enhanced Raman spectroscopy (SERS), X-ray diffraction (XRD), X-ray photoelectron spectroscopy (XPS), energy dispersive spectroscopy (EDS) and ultraviolet (UV)-visible spectroscopy, Fourier transform infrared spectroscopy (FTIR), atomic force microscopy (AFM), atomic absorption spectroscopy (AAS), dynamic light scattering (DLS), scanning and transmission electron microscopy (SEM and TEM) and high angle dark field (HAADF) (Ingham, 2015; Ealias and Saravanakumar, 2017; Sharma et al., 2022; Vijayaram et al., 2024).

5 Green synthesis: machine learning and *in silico* approaches

The GS of NPs depends on various parameters, such as the optimisation of the chemical processes involved in the synthesis, the required precision and their production. These steps are usually very expensive, labour-intensive, dependent and time-consuming. The synthesis processes also require control of reagent concentrations, temperature, mixing conditions and the reactor (Tao et al., 2021; Nathanael et al., 2023). Varying the type, amount and concentration of stabilising agents could lead to a change in the size of the NPs to be synthesised (Tao et al., 2021; Nathanael et al., 2023). Due to the progress and need for data collection and processing, artificial intelligence and machine learning have been integrated with nanotechnology in the synthesis and prediction of characteristic features of NPs (Shafaei and Khayati, 2020; Mekki-Berrada et al., 2021; Nathanael et al., 2023).

6 Factors affecting the synthesis

Various factors influence or determine the synthesis of NPs, including features, characterisation, application, types and concentrations of stabilisers, ionic stabilisers (citrate) and pH (Patra and Baek, 2015; Nathanael et al., 2023). Some of the other important parameters are the concentrations of the extracts and raw materials used, the pH of the solution, the temperature, the size of the raw materials and the process of synthesising the NPs (Patra and Baek, 2015).

Process of synthesis: There are different types of NP synthesis, namely, physical (arc discharge, mechanical grinding, electron beam lithography, etc.), chemical (chemical reduction of metals, electrolysis, microemulsion, etc.) and biological (with plant extracts, algae, enzymes and biomolecules, etc.). However, biological approaches to synthesise NPs are non-toxic and use environmentally friendly materials and are therefore environmentally friendly, efficient and more acceptable than conventional methods (Patra and Baek, 2014).

pH: Maintaining pH is an essential factor as it may be involved in the synthesis of NPs. The pH plays an important role in living organisms as it influences the basic processes and therefore requires optimal conditions for better functioning (Patra and Baek, 2014).

Temperature and pressure: It is also an important factor in determining NP synthesis. It can be observed that physical methods require about >350°C, while chemical methods require about 350°C or less. However, biological methods require lower ambient temperatures (<100°C). The temperature of the medium is crucial as it helps to determine the nature of the NPs (Patra and Baek, 2014).

Time: Time is one of the most important factors in the synthesis of NPs, as it controls the formation of NPs (quality and type), which depends on the time allowed for the reaction and incubation time. The time allowed for storage can influence the shelf life of the NPs and the aggregation of the NPs.

Biomolecules and functional groups: The functional groups (thiols, amines, sulphides, phosphines, carboxylic acids) have a major influence on the nature of NPs to be synthesised and can change the surface coating of the NPs. Therefore, the immobilisation of the groups will lead to the synthesis of the desired NPs (Shreyash et al., 2021).

Other factors: Plants and microorganisms produce secondary metabolites that serve as reducing and stabilising agents for the synthesis of NPs. Particle size, pore size and shape play an important role in determining the properties of NPs. It has been found that the melting point of NPs decreases with increasing particle size in the nanometre range (Akbari et al., 2011). Similarly, the light conditions (quality, exposure time and intensity) can alter the synthesis of NPs.

7 Applications of nanoparticles

There are various applications of NPs in different fields and sectors such as agriculture, environment, targeted drug delivery, cancer treatment, food and beverage industry and paints, etc. Some of these applications are described below.

Cancer treatment: Cancer is one of the biggest global challenges. Due to their anti-proliferative and cell death-inducing properties, NPs (AgNPs, AuNPs, etc.) are very actively used in the treatment of cancer. As they are small particles, they are easily circulated, bioavailable, soluble, and non-toxic and are distributed and transported by capillaries (Dikshit et al., 2021; Shreyash et al., 2021; Ying et al., 2022).

Targeted drug delivery: The use of nanoparticles as effective drug delivery systems is of great importance due to their size, bioavailability, continuous drug release, significant drug delivery capacity, prolonged circulation time, effective intracellular penetration and ability to protect the active ingredient from physiological barriers. The efficacy of cancer treatment can be improved by dynamically focusing drugs at preferred sites *in vivo* (Khatik, 2022). Biomaterials (growth factors with living cells) or bioinks based (quantum dots, polymeric micelles, gelatin methacrylate, etc.) on NPs have potential applications in tissue engineering, regeneration and treatment through artificial techniques such as human organs (Salahshour et al., 2024). Similarly, nanocomposites (microbial- and plant-based gums) can also be used for different therapeutic purposes (cancer, water treatment, etc.) (Dhanda et al., 2025).

Anti-microbial properties: GS-NPs are effective against a range of diseases caused by pathogens such as fungi, viruses and bacteria. They can reduce the likelihood of antibiotic resistance and prevent infectious diseases. This creates new opportunities for the improvement of environmentally friendly nanobased antimicrobials (Vanlalveni et al., 2021). AgNPs have been reported to be excellent against multidrug-resistant strains of *Pseudomonas aeruginosa, Bacillus subtilis, Staphylococcus aureus* and *Escherichia coli* (Roy et al., 2019).

Agriculture and environment: In agriculture, the use of nano-fertilisers has recently increased and attracted great interest (Dikshit et al., 2021). However, biofertilisers (TiO_2, SiO_2 including others) are preferred over fertilisers and the former can also be applied to plants using nanocarriers (Kumar et al., 2021; Zafar et al., 2024), taking advantage of the benefits of nanotechnology. The NPs are also used in bioremediation (metallic NPs), water purification (or wastewater treatment) (MgO, TiO_2 and ZnO), soil purification and detection of heavy metal NPs (arsenic, chromium, mercury) (Dikshit et al., 2021).

Food preservation, packaging, supplements and value addition: NPs (Ag-Cu, Au, Pt) are used in the food industry for the production, storage, packaging and transport of products. They increase shelf life, reduce the risk of microbial growth (nanocomposite of starch and sorbic acid), increase the absorption of vitamins, and vitamin-containing sprays with nanodroplets (Fe, Zn) as nano-nutrients and develop nanoparticles for smart packaging to trap oxygen and moisture absorbers (Dikshit et al., 2021).

Renewable energy: Renewable energy is another area where green synthesised NPs are very promising (Samuel et al., 2022). Nanoparticles are used to improve the efficiency and performance of solar cells, photocatalysts and energy storage devices. For example, green synthesised ZnO nanoparticles produced from papaya leaf extracts have been employed to improve the ability of solar cells to store light, resulting in higher energy conversion efficiency (Rathnasamy et al., 2017; Ali et al., 2023).

8 Limitations of green synthesis of nanoparticles

The common problem encountered in the NPs synthesis is the ability to control the size, regularity and shape of the particles (Shreyash et al., 2021).

Consistency: The use of plant extracts or plant calli can influence NP synthesis. The growth conditions such as the pH value and temperature of the plants used in the GS also affect the consistency of the synthesis of the nanoparticles. For example, the absorption peaks of plant extracts and calli in Ag nitrate solution for the AgNP production differ significantly, resulting in different properties (Ying et al., 2022).

Synthesis pathway: The basic technique involves the use of solutions of biological components (microbes, plants or their extracts) mixed with metal salts such that metals get reduced to produce NPs. As a result, the GS technique is in most cases very arbitrary and without any control over product quality (Pal et al., 2022).

Size and shape: During the manufacturing process, there is limited control over the shape and dimensions of the desired end product. The final dimensions of the NPs produced also depend on the starting solutions and stabilising agents used (Baig et al., 2021; Huston et al., 2021; Pal et al., 2022).

Commercial production: Green NPs are produced according to need and application, so the desired size also varies according to use thus limiting the scope for commercial purposes (Gupta et al., 2023).

Reaction time (RT): The RT varies depending on the biochemicals and biosynthesis pathways used. It can be shorter or longer, which affects the properties of the end product (Alharbi et al., 2022; Ying et al., 2022).

Stability: The stability of the NPs produced by GS is impaired. The biological materials may also contain impurities in the form of free radicals that affect their stability (Gupta et al., 2023). There is a need for standardisation of GS processes as batch-to-batch variations are observed in GS (Rogers and Jensen, 2019).

9 Conclusion and future prospects

Green synthesis enables efficient use of resources and cost efficiency. The nanoparticles produced by GS are highly biocompatible and can therefore be used safely as nanomedicines. Despite its importance, GS technology is subject to limitations in terms of scalability, reproducibility and standardisation. In conclusion, green synthesis is an important technique for the environment-friendly production of nanoparticles and represents a promising direction for sustainable nanotechnology.

Author contributions

AP: Conceptualization, Data curation, Resources, Writing–original draft, Writing–review and editing. AR: Data curation, Resources, Writing–original draft, Writing–review and editing. SG: Resources, Supervision, Validation, Writing–review and editing. SS: Conceptualization, Formal Analysis, Funding acquisition, Supervision, Validation, Visualization, Writing–review and editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnano.2024.1506665/full#supplementary-material

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