Review Article

Int J Pharma. Bio. Sci, Vol: 16, Issue: 4, 2025; 31-41

International Journal of Pharma and Biosciences

Content Available at www.lapinjournals.com ISSN: 0975-6299

ECO-FRIENDLY GREEN SYNTHESIS VERSUS CONVENTIONAL CHEMICAL METHODS OF NANOPARTICLES SYNTHESIS: IMPLICATIONS FOR BIOMEDICAL EFFICACY, SAFETY, AND APPLICATIONS

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Article History:Received:24.Sept.2025Revised: 14.Oct.2025Accepted: 26.Dec.2025

Abstract

Nanoparticles (NPs) have revolutionized the field of biomedicine, but their therapeutic potential critically depends on the methods used for their synthesis. Traditional chemical approaches, such as co-precipitation and sol-gel methods, allow precise control over NP size, shape, and crystallinity, making them highly effective and amenable to industrial-scale production. However, these methods often generate toxic by-products, utilize hazardous reagents, and consume significant energy, posing environmental and health risks. In contrast, green (biological) synthesis techniques employ eco-friendly reducing agents, including plant extracts, microorganisms, and bio-waste. This approach offers a safer, cost-effective, and environmentally sustainable alternative, providing improved biocompatibility and a better safety profile, largely due to natural bioactive surface-capping agents. This review compares conventional chemical and green synthesis methods of nanoparticles, evaluating their effects on physicochemical properties and biomedical performance. Additionally, it provides a detailed discussion of their applications in areas such as antimicrobial activity, drug delivery, and imaging, highlighting the superior safety and lower toxicity of green-synthesized NPs. Overall, despite the technical precision of chemical methods, green synthesis techniques demonstrate lower environmental impact, reduced toxicity, and enhanced safety, making them the most desirable and sustainable approach for developing nanoparticles for both biomedical and non-medical applications, including environmental remediation and sustainable agriculture.

Keywords: *Nanoparticle, Greensynthesis, Chemicalsynthesis, Biomedical efficacy, Biocompatibility, Toxicity, Drug delivery, Physicochemical property, Environmental safety, Public health.*

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DOI: https://doi.org/10.22376/ijpbs.v16i4.134

1. INTRODUCTION

Nanoparticles are substances that have a dimension of at least 100nm and have special physical, chemical, and biological characteristics because their size is small and their surface area is high [1,2]. Their types may vary in terms of composition (metal, metal oxide, polymeric, carbon-based), structure (core-shell, hollow, composite), and source (natural, synthetic) [1,2,3].

Nanoparticles have been synthesized physically using laser ablation and evaporation conditioning as well as through chemical processes such as chemical reduction, sol-gel, and co-precipitation [4]. Although these techniques provide a great way to control the size and morphology of particles, they can be rather demanding in conditions and consume large amounts of energy1. They generate dangerous by-products, although they are as precise as structure, and use harmful reagents [5]. These disadvantages raise concerns about the biomedical and environmental risks associated with the use of poisonous chemicals [6]. Also, waste generation that not supports ecological safety [7]. Thus, even though effective, such methods of synthesis have deadly drawbacks with respect to biomedical application.

The restrictions of the conventional synthesis procedure prompted the emergence of the green or microorganism's synthetic technique that uses plant extracts, microorganisms, enzymes, or other biological substances as a reducing and stabilizing reagent. This method is viewed as environmentally friendly, inexpensive, and able to operate within slightly harsh experimental parameters1. Also, it leads to better biocompatible and less toxic nanoparticles in relation to the traditional methods. The researchers have emphasized the fact that such a strategy lowers environmental and biomedical risks, so it is a more sustainable option. Moreover, it reduces the ecological risks since it does not produce toxic waste during production [7]. Singh et al., 20208 also highlighted its potential in the further Integrity development of nanoparticle production that could be safely used in the medical field. All of these benefits have encouraged the transition to green synthesis as a cost effective and sustainable method of obtaining nanomaterials for biomedical uses. Nanoparticles have greatly influenced the field of biomedicine through the creation of improved opportunities in drug delivery, imaging, and diagnostics, antimicrobial therapies, tissue engineering, etc.. The fact of their nanoscale small size provides easy cellular uptake and proximity to the biomolecules, contributing to the efficiency of the therapeutic part and the biological activity1. Additionally, surface modification technology has enabled precision of therapy with limited side effects, and it has been expanded into multiple clinical use scenarios [5,2]. Specifically, green-synthesized nanoparticles have been mentioned to offer better safety profiles as well as functional adaptability than their traditionally synthesized counterparts [4,1]. Such a green strategy values extensive toxicity reduction, optimal therapeutic compatibility, and is connected to the idea of sustainability [5,6]. Scientists have also noted that hazardous byproducts are avoided and increase biomedical usefulness7. The hope of green nanoparticles in the field of trans-media medicine was also emphasized by Singh et al., 20208. All these facts prove that the shift to green synthesis has intensified the arch of use of nanoparticles in medicine, focusing more on sustainability, insight, and effective treatment [3].

2. APPROACHES FOR SYNTHESIZING NANOPARTICLES

Nanoparticle synthesis is broadly categorized into chemical (conventional) and biological/green (eco-friendly) methods, each with distinct mechanisms, advantages, and limitations.

2.1 Chemical Synthesis of Nanoparticles

The general approach to chemical synthesis of nanoparticles is to reduce metal precursors (usually metal salts) in solution with a strong reducing agent (e.g., sodium borohydride or hydrazine) and stabilize or cap the particles with surfactants and other polymers [9]. A number of popular chemical methods have been mentioned, such as sol-gel production, co-precipitation, hydrothermal treatment, micro emulsion processes, and colloidal [10]. The success of these processes is highly contingent on process parameters, in which the temperature, pH, precursor concentration, and reaction time have a significant role in the morphology and physicochemical properties tuning of nanoparticles [11,12]. It has been highlighted by researchers that minor variations of these parameters can have bipolar impacts on particle size distribution, stability, and functionality, and, hence, their applicability to biomedical and industrial purposes [13,14].

Some of the benefits of chemical synthesis of nanoparticles include high degree of control of the size, shape, and monodispersity of the nanoparticle. This technique enables accurate adjustment of the particle properties that leads to consistent and repeatable results. Also, chemical synthesis of industrial production can be scaled, allowing large-scale production of nanoparticles based on optimized protocols [9,10,12].

2.2 Biological/Green Synthesis of Nanoparticles

Biological hosts like plants, bacteria, fungi, algae, or yeast, or bio-waste are natural reducing and stabilizing agents that are used to prepare nanoparticles greenly [15]. Particularly, enriched plant extracts have been identified to exhibit successful mediation attenuating metal ions, whereas the same enriched with biomolecules, such as polyphenols, flavonoids, proteins, and capping nanoparticles to improve the stability of these particles [16]. Likewise, bacterial, fungal, or algae metabolites serve as both reducing (and capping) agents, which allows nanoparticles to be produced in mild and ambient conditions and make the process environmentally friendly and sustainable [17,18].

There are several benefits to green synthesis of nanoparticles, such as being environmental friendly and sustainable. It typically involves natural reducing and stabilizing agents such as plant extracts or microbial components, and this reduces the cost of the process and also reduces toxicity. Such an approach is especially applicable to biomedical and environmental remediation because it is safe and cost-effective [15,16,17].

Various biomolecules are employed in the biological apparatus, such as enzymes, proteins, and polysaccharides, which act concurrently as reducing and capping functions in the creation of nanoparticles; thus, leading to the formation and stabilization [15]. Individual biochemical mechanisms behind the mentioned process have varied according to the organism and extract structure, indicating how flexible and complicated green synthesis protocols are [16,18].

Green synthesis of nanoparticles faces challenges in reproducibility and scalability due to the biological diversity in nanoparticle formation. The inherent variability seen in biological sources results in differences in size, shape, and yield, making standardization difficult. Also, understanding of the biochemical pathways involved is still evolving, limiting the predictability and consistency of green synthesis methods [15,16].

Hence, chemical synthesis offers precision and scalability but raises environmental concerns, while biological/green synthesis provides a safer, eco-friendly alternative with growing potential, though challenges. Both approaches are vital for advancing sustainable nanotechnology.

3. COMPARATIVE ANALYSIS OF BIOLOGICAL AND CHEMICAL SYNTHESIS

Modern materials and chemical production heavily rely on both biological and chemical synthesis; nevertheless, they are different in their effectiveness, scale, reusability, adherence to environmental sustainability, and consumption of resources.

The vast majority of chemical synthesis relies on well-developed processes with higher yield that can generate nanoparticles using the known chemical starting material, a catalyst, and a solvent [19]. They are known to be highly valued due to their ability to be reproduced and scaled, and have become a staple of the industry that produces chemicals [20]. Although these have advantages, they tend to use significant amounts, use vast resources that cannot be replenished, and lead to the creation of dangerous by-products [21]. These disadvantages have cast doubts over their future environmental sustainability and possible long-term economic car tax liabilities [22,23].

Biological synthesis, including bio-manufacturing and green synthesis, employs living organisms and/or enzymes, or biological extracts as the biological systems to create application chemicals and materials [19]. It is considered more environmentally friendly as it utilizes renewable feed-stocks and has a substantially mild nature of operation, thus lowering energy requirements and formation of toxic waste [24]. In spite of these strengths, however, biological techniques can be limited by factors such as efficiency, scale, and reproducibility, and this may be especially problematic when it comes to generating intricate molecules or large-scale products [25,9]. Research individuals have also mentioned that biological synthesis-based developments to achieve an industrial level of consistency still present a large challenge as compared to usual chemical synthesis [26].

3.1 Efficiency, Scalability, and Reproducibility

- Chemical synthesis provides great productivity and reproducibility, particularly for highly optimized processes. Its large-scale use in industry is straightforward, and some more complex or greener systems of catalysis, typically capable of much wider use, are under development [19,20,23].
- Biological synthesis can show high productivity on select items, e.g., antibiotics and organic acids; however, in such instances, its implementation is typically restricted because of metabolism complexity and inherent variability in biology, which affects the qualities of reproducibility and scalability [19]. Synthetic biology and cell-free systems are the most recent innovations that will help overcome these obstacles, enhance consistency, and provide more controlled production processes [25,24]. But even with these technological advances, it is still a major challenge to rank medium-scale and cost-efficient manufacturing of many targets of biological derivations [9,26].

3.2 Environmental Impact and Sustainability

- Fossil fuels, hazardous chemicals, and energy-intensive processes form a frequent basis of chemical synthesis, leading to a substantial amount of greenhouse gas emissions and pollution of the environment [20]. Even though recently, process intensification and novel methods of catalysis corresponding to the reduction of these environmental consequences have been created, it is still difficult to completely eliminate these effects [21,22,23].
- Biological synthesis can be regarded as a more efficient process than usual approaches because biology involves renewable origin materials and produces less toxic by-products in the process of nanoparticle synthesis [19]. The usage of bio-waste or green extracts can also lead to a positive effect on the environment, where the means of green synthesis are built on the use of plant extracts or bio-waste [25,9]. These techniques fit the general principles of sustainable development since they reduce resource use and improve the ecological suitability of the nanomaterial production [26].

3.3 Cost, Energy Consumption, and Resource Use

- High energy use and the cost of the raw materials, especially being dependent on non-renewable resources, can impose costs on chemical synthesis; nonetheless, on an industrial scale, it can be cost-effective20. Furthermore, it assists in ranking management of waste materials and compliance standards with the environment, while least contributing to the overall operational costs [21,22,23].
- The synthesis via biology can lower the cost by using low-cost renewable feedstock's and also working under less severe temperatures and intensities [19]. Nevertheless, because of reduced yield of the products, increased processing time, and the necessity to acquire special bioreactors and downstream processing technologies, such a benefit may be compensated [24,25]. This can consequently cause a higher cost of production based on the complexity and size of the operation of the product [9,26].

Overall, Chemical synthesis excels in efficiency, scalability, and reproducibility but faces sustainability and environmental challenges. Biological synthesis offers greener, more sustainable alternatives, though further advances are needed to match the industrial robustness of chemical methods.

4. PHYSICOCHEMICAL PROPERTIES OF NANOPARTICLES AND THE INFLUENCE OF SYNTHESIS ROUTE

4. 1Morphology

Morphology refers to the physical shape of nanoparticles (e.g., spheres, rods, cubes). Conditions such as temperature, solvent, and capping agents allow fine control over morphology. For instance, magnetite nanoparticles produced by co-precipitation or thermal decomposition exhibit different shapes and surface structures, which subsequently affect their magnetic and functional properties [27,28,29,30].

4. 2 Size Distribution

Size distribution describes the uniformity and spread of nanoparticle sizes within a sample. Chemical reduction methods such as sol-gel and thermal decomposition typically produce nanoparticles with narrow, well-controlled size distributions due to homogeneous reaction conditions [7,28]. In contrast, biological/green methods often yield broader size distributions because of variability in biological reducing agents and environments [31,32]. Additionally, monodispersed nanoparticles can be synthesized using electrochemical and photochemical processes, which offer precise size control [33].

4. 3 Crystallinity

Crystallinity refers to the degree of structural order in nanoparticles and significantly influences their physical and functional behaviour [27]. The crystallinity depends strongly on the precursor material and reaction conditions, including low- and high-temperature chemical reduction methods [34]. Green synthesis may sometimes yield lower-order or mixed crystal phases, although some iron oxide nanoparticles produced via green routes show crystallinity comparable to those produced through conventional methods [28,29]. Poor crystallinity can alter behavior such as weakening magnetic or catalytic performance. Techniques like X-ray diffraction (XRD) are used to assess crystal quality and domain size.

4. 4 Surface Chemistry

Surface chemistry can be controlled through capping agents (e.g., surfactants, polymers) that stabilize nanoparticles during chemical synthesis [28]. Capping influences the reactivity and overall surface behavior of nanoparticles [32]. Green synthesis uses natural bioactive molecules (e.g., peptides, phytochemicals) that adhere to the nanoparticle surface, enhancing biocompatibility and therapeutic interactions compared to chemically synthesized counterparts [34].

4. 5 Influence of the Synthesis Route

• Chemical routes

Produce nanoparticles with controlled shape, size, crystallinity, and uniform, stable surface chemistry, offering a high level of precision [27,28,29].

• Green/biological routes

Provide eco-friendly nanoparticles with bioactive surfaces but may result in broader size distributions and varying degrees of crystallinity depending on the natural extract used [32,34,35,36].

To conclude, the synthetic route plays a central role in defining nanoparticle morphology, size distribution, crystallinity, and surface chemistry-ultimately determining stability and functionality. While chemical methods offer high precision, green synthesis provides biofunctional surfaces through environmentally friendly approaches.

5. APPLICATIONS OF NANOPARTICLES

Nanoparticles (NPs) have revolutionized biomedicine, where they have provided cutting-edge solutions in the fields of therapy, diagnostics, and bio sensing. The route of their synthesis (green/biological) or chemical one is also of great impact on the biomedical efficacy, safety, and even mechanisms of action. Moreover, gained extensive application in non-medical industries, and the application and advantages of nanoparticles highly depend on the type of synthesis employed either, reduction-based or green (biological) synthesis.

5. 1Biomedical Applications

5. 1.1 Antibacterial, Antifungal, Antiviral, Antioxidant, and Anti-inflammatory Properties

- Antimicrobial Activity

  The NPs have a potent antibacterial, antifungal, and antivascular effect that causes membrane disruption, the production of reactive oxygen species (ROS), and cellular metabolism. To improve upon these effects, green-synthesized NPs, which tend to have bioactive plant or microbial molecules at their terminals, are possible to reduce toxicity to human cells (repeated below) [37,38].
- Antioxidant and Anti-inflammatory Effects

  The antioxidant and anti-inflammatory activity of many NPs, especially those synthesized through green procedures, is attributed to surface-bound phytochemicals or proteins, which hunt down the free radicals and regulate the preferences of the inflammatory response38.

5. 1.2 Drug Delivery Systems, Targeted Therapy, Imaging Agents, and Biosensors

The advantageous effect of nanoparticles against microbes has been noted to be mainly because of their ability to disrupt the microbial membranes, form reactive oxygen species (ROS), and disrupt the metabolism of the cells [37]. Green synthesis is able to substitute conventional nanoparticles that have a limited antimicrobial capacity or biocompatibility with nanoparticles due to increased bioactive surfaces [37].

- Nanoparticles and their targeted Therapy:
  - Solid Lipid Nanoparticles (SLNs) and Nanostructured Lipid Carriers (NLCs): Lipid-load particles which can entrap hydrophilic and lipophilic drugs, enhance their bioavailability and are used as target drug delivery in psoriasis and other inflammatory skin diseases [39].

  - Metallic nanoparticles: Such as gold or silver nanoparticles, used for their unique optical and magnetic properties, enabling targeted drug delivery and imaging, especially in cancer diagnosis and therapy [40].
  - Protein-based nanoparticles: These are biocompatible and biodegradable nanoparticles which can be used to deliver anticancer drugs and therapeutic proteins [41].
  - Chitosan-based nanoparticles: Chitosan-based nanoparticles are biocompatible and specific in targeting, and can be used in cancer, gene delivery, and mucosal drug delivery [42].
  - Mesoporous nanoparticles and carbon nanotubes: They are employed due to their high surface area and large drug load capacity but primarily in cancerand neurodegenerative diseases [43].
- Imaging Agents and Biosensors:
  Nanoparticles are also useful contrast agents for MRI, CT, and fluorescence, as well as remarkably sensitive biosensors, due to their distinctive optical and magnetic properties [44,45]. The two nanoparticles applications that are highly desired include the nanoparticle of gold and the iron oxide due to their surface properties, which may further be modified with functionalization to provide a better contrast and sensor sensitivity [46]. Green synthesis enhances this with extra biocompatibility and minimized background toxicity, making nanoparticles less dangerous and more applicable in terms of biomedical imaging [38].

5.1.3 Mechanisms of Therapeutic Effects and Cellular Interactions

- Cellular Uptake and Trafficking:
  The main pathways through which nanoparticles enter cells are through multiple endocytosis pathways, and they include clathrin-mediated, caveolae-mediated, Macropinocytois and phagocytosis. Clathrin-mediated endocytosis combines a ring around the cell membrane in the form of clathrin-coated pits, which subsequently invaginate to create a pinched off vesicle within the cell, also employing such an invagination for receptor-mediated uptake [44,47,48], an another significant uptake pathway is powered by caveolin proteins. Hoshy Macropinocytosis and phagocytosis entail the uptake of bigger particles or volumes of extracellular fluid that is an action-dependent mechanism commonly embraced by specialized cells such as macrophages [47]. The intake performance and routes are dependent on the size, shape, surface chemistry, and cell type of nanoparticles [44,48]. Natural ligands on green-synthesized nanoparticles potentially induce specific cellular uptake routes and, among off-target effects, thereby enhancing cellular internalization specificity [44]. Upon endocytosis, nanoparticles are normally transported by endosomes and lysosomes, and this has a repercussion on the cellular fate and downstream action of the nanoparticle.
- Intracellular Fate and Mechanisms:
  After internalization, nanoparticles can settle in different organelles (endosomes, lysosomes, mitochondria, and the nucleus) and deliver drugs or cause an effect in response to therapeutic requirements [48,49]. Nanoparticles have an additional layer on their surface, a biocorona, composed of adsorbed biomolecules formed in biological sites, which also affects cellular reactions, immune challenges, and therapies [37,44]. The fate of nanoparticles depends on intracellular trafficking processes, and the particles are commonly enclosed in vesicles, including endosomes, lysosomes, and others, but some of the particles may bypass the vesicles and contact organelles [44,48]. Such intracellular localization controls the effectiveness and safety of nanoparticle targets by influencing the release kinetics, the generation of reactive oxygen species, and the stimulation or muting of cellular signaling [37,43].
- EfficacyandSafety:
  Chemical synthesis techniques offer the advantage of reproducibility in nanoparticle generation, with precise control over size and shape; however, a major disadvantage is the potential cytotoxicity caused by residual chemicals and toxic byproducts [44]. In contrast, green synthesis employs biocompatible capping agents derived from biological sources, generally resulting in safer nanoparticles with improved therapeutic indices and greater suitability for biomedical applications [38].This green draw of the synthesis is in line with a larger shift in the development of safer, greener, and efficacious nanoparticles in clinical [38,44].

5.2 Non-medical Applications

5.2.1 Industrial Applications

- Catalysis:
  Further uses of nanoparticles have been efficient catalysts in chemical manufacturing and energy production, as well as environmental remediation [50,51]. Nanoparticles synthesized with green can be based on plant extracts or agricultural waste; such nanoparticles have catalytic properties comparable to those of chemically synthesized ones, but they are less toxic and use less expenditure of energy [52,53]. All these properties render green-synthesized nanoparticles a more sustainable and appealing choice to employ large-scale industrial applications, which are in line with attaining environmental and economic priorities.
- Materials and Electronics:
  Silica and metal nanoparticles can be widely used in electronics, paints, and coatings with

reference to their peculiarities in physics and chemistry[51]. The technique of green synthesis based on agricultural waste, e.g., rice husk leaf transporter or bamboo leaf ash, is cheap and has a lower environmental emission profile than the established chemical synthesis pathways. These green technologies aid in minimizing the production of hazardous wastes and minimizing the production costs, which are appealing in the production process of products that are eco-friendly [52].

5.2.2 Agricultural Applications

- Nano fertilizers and Nano pesticides:
  Nanoparticles make the nutrition delivery system, crop protection, and soil quality more effective and targeted, as they allow agrochemicals to be effective [55,56]. Nanoparticles manufactured through synthesis using plants, bacteria, fungi, or agricultural waste are preferred because they are less toxic, have better biocompatibility than conventional formulations [57,58]. Such green nanoparticles also help to limit the consumption of chemical pesticides and fertilizers to decrease environmental contamination and facilitate sustainable food security [59,60,61]. Also, they can be used as an ecologically friendly substitute in the current farming since their application contributes to the health of the soil and the balance between microorganisms [15,62,63].
- Phytopathogen Management:
  Biogenic nanoparticles have an increased antifungal and antibacterial activity that aids in managing the disease of plants and lower chances of resistance development in relation to using conventional agrochemicals [55,56]. They also cause less negative effect on the environment because of their natural origin and biodegradability [57,58]. Such nanoparticles also provide a very beneficial solution to addressing the issue of pathogens because they are safe and more sustainable in the agricultural sector since they can manage emerging disease causes but with little harm to the ecosystems [59,60,63].
- Smart Agriculture:
  Green nanoparticles find more and more applications in the field of biosensors to monitor soil and crops, which allow precision farming and control by allowing real- time monitoring of soil characteristics, nutrients, pathogens, and the environment [55,58]. These biosensors aid in efficient utilization of resources when used to offer the right information that aids farmers to spread the fertilizers, pesticides, and water more optimally, thereby increasing the crop yield with a low environmental impact15. Green-synthesized nanoparticles are biocompatible and sustainable due to their eco-friendliness, thereby making them the best agricultural monitoring technology [55].

5.2.3 Environmental Applications

- Water and Soil Purification:
  The removal and suitability of nanoparticles in removing heavy metals, dyes, pesticides, and other pollutants have been shown to be very effective in environmental cleanup because of their usage not only in water and harmful soils but also within aquaculture settings [50,51]. Agricultural waste nanoparticles and other greener-synthesized nanoparticles are safer to the ecosystem because of their biocompatible nature, which also has better adsorption capacity and degradation than other widely used synthetic nanoparticles [52,64]. These are environmentally friendly nanoparticles that minimize the effects of secondary pollution and aid in sustainable purification processes of water and soil [15,43,53,65].
- Pollution Control and Waste Management:

Green nanoparticles are important with regard to pollution control and waste management because they aid in minimizing environmental degradation by supporting the principles of the circular economy. They amplify the use of agricultural and industrial wastes, as it will decrease the size of landfills [50,51]. Green nanoparticles can provide a clean solution to waste-to-resource transformation as they can convert waste materials into useful nanomaterials, and this newly produced nanoparticle contributes to environmentally friendly and resource-saving practices [52,53,64].

6. SAFETY AND TOXICITY

The risk and safety of nanoparticles (NPs) depend on synthesis technology, size, shape, surface characteristics, and their interaction with the customary biological systems. The green (biological) and the chemical synthesis paths result in NPs with different toxicity profiles, biocompatibility, and environmental effects.

6. 1In Vitro and In Vivo Toxicity Profiles

- The cell cultures and animal models are usually more toxic to chemical NPs than the biological NPs. An illustrative case is chemically produced copper oxide NPs, which treated the cell cultures of plants with a higher toxic and oxidative effect compared to the green-synthesized NPs, probably because there were no natural capping agents that decreased those detrimental effects [66].
- Biological NPs (e.g., milk -derived nanovesicles, plant-capped NPs) tend to be less toxic in in vitro and in vivo models. Nevertheless, all the toxicity screening in the animal model is necessary because the in vitro data may not necessarily translate to in vivo. The effects produced as a result of biological NPs on the organs or immune system might also be [66,67].

6. 2Influence of Size, Shape, Surface Modification, and Charge

- Size and Surface Charge
  The cyclic nature of specific biological molecules is more likely to interact with smaller nanoparticles, and the probability of penetrating tissues and cells with them increases, and, thus, the effect of the substances inside is increased [68,69,70,71]. Also, increased surface charge is more toxic, since increased surface charge causes improved toxic particles to have stronger electrostatic interaction with the components of the cell and consequently increase cellular uptake and adverse effects [72,73]. This increased toxicity regardless of the mode of synthesis but, surface properties such as charges have a major influence on biological reaction.
  - Shape and Surface Modification

  Compared to rod- or fiber-shaped nanoparticles, spherical shaped nanoparticles contaminating biological membranes are less likely to cause cellular damage and trigger toxicity in people, and hence, relatively harmless [66,68,70]. Nanoparticles whose shapes are long or have high aspect ratio (i.e., rods, fibers, etc.) are more likely to lead to elevated levels of cytotoxicity, inflammation, and cellular stress in part due to increased internalization. The presence of surface coating serves to reduce toxicity by fixing nanoparticles and preventing unwanted interactions between nanoparticles and cells and biomolecules, which increase biocompatibility [71,66]. Such surface modifications can overcome the innate shape- related toxicity as size effects when the aggregation and internalization of nanoparticles, and cellular intake mechanisms, are regulated [70].

6. 3 Biocompatibility, Bio distribution, and Excretion

- Biocompatibility:
  Natural molecule-capped biological nanoparticles are less reactive and tolerated by the biological systems, resulting in reduced immune responses and cytotoxicity [66,67]. Nanoparticles are stabilized by the capping agents based on a biological source, e.g., proteins, phytochemicals, and enzymes, and increase biocompatibility [75,76]. Such types of natural capping molecules regulate surface chemistry and topography, producing less toxic and more friendly to biological surfaces nanoparticles [77]. Moreover, bioactive nanoparticles capped with the use of bioactive phytochemicals can confer antimicrobial and anticancer effects to the nanoparticles and retain safety profiles enabling their use in the medical field [78,79]. On the whole, the introduction of natural biological capping agents plays the major role in the manufacture of effective resistance and biocompatible nanoparticles, which have biomedical applications[66,80].
- Bio distribution and Excretion:
  The biological barriers crossed by nanoparticles can be deposited into different body parts, including the liver, lungs, and brain, and this affects how nanoparticles are distributed in different body parts81. Most importantly, the circulation of nanopartices, their location in the organism, and the mechanism of their excretion depend on the surface chemistry and size of such particles [80]. Nanoparticles that possess natural biomolecule-based coatings, as synthetic biologically, may be more easily cleared out of the body via more biomolecule-specific recognition and processing by the body and minimise long-term retention and potential toxicity [81,80].
- Pharmacokinetics
  Post-identification, which modifies NP identity through the protein corona (layer of biomolecules adsorbed on the surface of the NPs), alters the behavior of the particles in terms of distribution, uptake by cells, and clearance [80].

6.4 Long-term Effects on Humans, Animals, and the Environment

- Chemical nanoparticles can be retained both in the environment and in other living organisms, which can be chronically toxic, inflammatory, and genotoxic [82,81]. The accumulation of nanoparticles in essential organs or the disturbance of the ecological system is also under study due to the long-term effects of these nanoparticles, although concerns about this issue exist [83,80]. Their longevity poses great concerns about their safety and environmental hazards, thus the necessity of thorough evaluation of their life cycle and their interrelationship with biological and environmental compartments [81,82].
- Biological nanoparticles are more broadly considered safer to be used in the long term as they have biocompatible surfaces and biogenic origin, which is less likely to experience toxicity and persistence of environmental effects [66,67]. Nevertheless, to gain deep insights into their environmental and health outcomes, they remain an active subject of study as large-scale and systematic research continues to develop [81,83,80]. Their life cycle, further degradation, or interactions with the ecosystems have to be evaluated carefully to establish their safe and long-term sustainable exploitation [67].

Overall, biological (green) nanoparticles generally offer improved safety, lower toxicity, and better biocompatibility compared to chemically synthesized nanoparticles, largely due to their natural surface coatings. However, all nanoparticles require careful assessment of their size, shape, charge, and long-term effects to ensure safe biomedical and environmental use.

CONCLUSION

Nanoparticles that have been synthesized using green methods have become a revolutionary process in the field of biomedicine, with obvious benefits over chemical synthesis. More biocompatible, less toxic, and eco-friendly than other nanoparticles, green-synthesized nanoparticles are generating the use of plant extracts, microorganisms, or other biological matter. This is a green process which involves the complete or significant decrease in the use of hazardous chemicals, or the Nano product is safer than previously manufactured.

Bio medically, green-synthesized nanoparticles exhibit good antimicrobial, antioxidant, anticancer, and drug delivery technologies, including many of the natural capping agents on their host microorganisms. They offer greater therapeutic efficacy and reduced immune reactions and adverse responses because these natural coatings are not only superior but also safer and less harmful compared to other 2F-4F LRRs or - LRP8, which is why they are very suitable in delicate complete medical settings. In addition, green synthesis is economic, scalable, and mild- conditioned, which promotes affordable and sustainable healthcare solutions.

Although chemical synthesis enables tight control of nanoparticle characteristics, it is usually associated with harmful reagents and wastes that might restrict biomedical safety and use. As opposed to that, green synthesis complies with the ideals of green chemistry, so the nanoparticles that will be obtained as a result will not only be effective but also harmless to be used in humans and the environment over a long period.

Overall, it could be concluded that the incorporation of green synthesis in Nano medicine is highly essential to developing safer, more effective, and sustainable biomedical technologies and therefore is theoretically the preferred technique to be used in the nanoparticle development in healthcare in the future.

FUNDING

No funding was received for this study.

ACKNOWLEDGEMENT

The authors sincerely thank the Department of Biotechnology, Sathyabama Institute of Science and Technology, Chennai, Tamil Nadu, 600119, India, for providing the necessary facilities and support to carry out this work. The authors also express their gratitude to the Faculty of Allied Health Sciences – Laboratory Medicine, Sri Ramachandra Institute of Higher Education and Research, Chennai, Tamil Nadu, 600116, India, for their valuable guidance and academic assistance during the preparation of this review article.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

INFORMED CONSENT AND ETHICAL STATEMENT

Nil

AUTHOR CONTRIBUTION

Sudhir J contributed to the conceptualization, literature collection, and writing of the review article. He prepared the primary draft and finalized the manuscript content.

Sudharsun M assisted in literature compilation, data organization, and manuscript editing. He also contributed to refining the structure and clarity of the review.

Jesia Persis Preethi contributed to the evaluation of the manuscript flow and coherence. She also assisted in reviewing and refining the final version of the article.

Sudha Srikesavan S provided academic guidance, manuscript corrections, and valuable insights for improving content quality and presentation.

Usha Nandhini S guided the overall conceptual framework and critically reviewed the manuscript. She supervised the work process and served as the corresponding author.

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