REVIEW ARTICLE

Developments in the Green Synthesis of Medicinal Nanoparticles: From Benign Solvents to Bio-assisted Sources

Gulrana Khuwaja*

Department of Pharmaceutical Chemistry and Pharmacognosy, Jazan University College of Pharmacy, Jazan, KSA.

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ABSTRACT

This review explores the advancements in green synthesis methodologies, focusing on the utilization of bio-assisted sources and benign solvents for the production of pharmaceutical nanoparticles. We discuss the significance of solvent systems in synthesis processes and highlight water as an ideal and accessible solvent. Various examples of nanoparticle synthesis in aqueous media are presented, including gold and silver nanoparticles produced *via* laser ablation. Additionally, we delve into the emerging field of "green" synthesis, which encompasses routes utilizing water as a solvent system and natural sources/extracts as primary components. Notably, ionic liquids are discussed as promising solvents for nanoparticle synthesis, offering unique advantages such as tunable properties and broad temperature ranges. Furthermore, the potential of supercritical fluids, particularly carbon dioxide and water, as solvent systems for nanoparticle synthesis is explored. Nanoparticles have numerous uses in the pharmaceutical and medical industries. We hope to shed light on environmentally acceptable and sustainable methods for synthesizing nanoparticles with this thorough review.

Keywords: Benign solvents, Green synthesis, Nanoparticles, Bio-assisted sources, Ionic liquids.

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INTRODUCTION

Recent advancements in nanotechnology have made significant strides, particularly during the process of creating metal nanoparticles (NPs).[1] Among the different techniques investigated, green synthesis has shown promise because of its affordability, scalability, and environmental friendliness.[2] This review aims to delve into the challenges associated with green techniques for synthesizing and evaluating metal nanoparticles, pharmaceutical applications, and prospects in this field. Key factors influencing green synthesis, such as precursor selection, reaction conditions, and stabilizing agents, are thoroughly examined. Additionally, techniques for characterizing green-synthesized nanoparticles, including spectroscopic, microscopic, and physicochemical methods, are reviewed. Furthermore, the possible uses of environmentally produced metal nanoparticles in a variety of fields, including catalysis.[3] medicine.[4] and environmental remediation[5] are underscored. Finally, future directions and emerging trends in metal nanoparticles are discussed in green synthesis.

Nanoparticles (NPs) boast unique because of their large surface-to-volume ratio and physicochemical features, rendering them attractive for diverse applications in industries ranging from electronics to medicine and catalysis. Traditional methods for synthesizing metal nanoparticles often involve chemical reduction or physical processes, which frequently entail the use of hazardous chemicals and energy-intensive procedures, leading to environmental pollution and health risks. In contrast, green synthesis presents a sustainable alternative by leveraging natural sources such as microorganisms, biopolymers, and plant extracts as agents for reduction and stabilization. This approach mitigates environmental impact and yields biocompatible nanoparticles suitable for biomedical applications.[6] The practical utilization of nanoparticles made of metal, due to their distinct characteristics, particles smaller than 100 nm are often used.[7-10] A range of chemical and physical procedures are currently employed for synthesizing metal nanoparticles, enabling the production of particles with tailored characteristics.[11-14] Nonetheless, these conventional synthesis methods tend to be costly, labor-intensive and pose potential risks to the natural world and living things.[15,16] For this reason, it is evident that a different, safe, economical, and ecologically friendly method of producing nanoparticles is required.[17-19]

Author for Correspondence: *Gulrana.khuwaja@gmail.com*

Current investigations have revealed the capacity of various biological systems, which include algae and plants,[20] diatoms,[21-22] bacteria,[23] yeast,[24] fungi,[25] and human cells,[26] to use the reductive qualities of the proteins and metabolites found in these organisms to transform inorganic metal ions into metal nanoparticles. Notably, harnessing plants for nanoparticle synthesis presents distinct advantages compared to different biological systems. Plants are a desirable platform for the synthesis of nanoparticles due to their cost-effectiveness, scalability, safety concerns, and shorter manufacturing times.[27]

Green-synthesized nanoparticles hold promise for various pharmaceutical applications due to their eco-friendly production process and potential therapeutic properties. These nanoparticles can act as drug delivery systems, allowing the precise and regulated delivery of medicinal substances to bodily locations, thereby enhancing drug efficacy and minimizing adverse effects. Additionally, green-synthesized nanoparticles exhibit antimicrobial properties, making them valuable candidates for combating drug-resistant pathogens and controlling infections. Furthermore, these nanoparticles can be utilized in diagnostic imaging techniques, providing high-resolution imaging of biological structures for early disease detection and monitoring. Overall, the eco-friendly synthesis and diverse therapeutic properties of green-synthesized nanoparticles position them as valuable assets in pharmaceutical research and development.

Synthesis of Metal Nanoparticles Using Plant Material

It has long been recognized that plants can lower metal ions both internally within various organs and tissues and outwardly on their surfaces.[28] This capability has led to the practice of phyto mining, where certain plants, especially those that are utilized to recover valuable metals from terrain that would otherwise be economically unviable for regular mining procedures due to their powerful metal ion hyperaccumulating and reductive properties. Phyto mining involves the uptake and accumulation of metals by plants, which can then be retrieved through processes like sintering and smelting after harvesting. Interestingly, research on the bioaccumulation of metals in plants has shown that these metals are frequently deposited as nanoparticles. *Medicago sativa* (alfalfa) and *Brassica juncea* (mustard greens) are two examples and have demonstrated the ability to accumulate silver nanoparticles measuring around 50 nm in high concentrations, up to 13.6% of their own weight when grown in the presence of silver nitrate.[29] Similarly, living plants have been found to harbor gold icosahedra measuring 4 nm, while *Iris pseudacorus* (yellow iris) grown in substrates containing metal salts showed the presence of semi-spherical copper particles measuring 2 nm in size.[30-31] While whole plants can act as systems that are efficient in producing metal nanoparticles, however there are obstacles in the way of their practical implementation.

Plant-synthesized nanoparticles can differ in size and form based on where they are found, which can be impacted by changes in the concentration of metal ions in various tissues.

This variability could affect the deposition of metals around current nanoparticles and the start of fresh nucleation processes.[30] The variable morphology and size of nanoparticles produced from whole plants may restrict their use in applications where precise morphologies and sizes are needed. Low recovery yields are also a result of the considerable difficulties involved in the extraction, separation, and purification of nanoparticles from plant material.

To overcome these challenges, *in-vitro* approaches have been produced in which plant extracts are used to create nanoparticles through the bio-reduction of metal ions. By modifying variables like pH and temperature, these techniques provide more control over the size and shape of nanoparticles while also streamlining the purification procedures. Importantly, the reaction occurs much more rapidly compared to synthesis within whole plants, as there is no delay for metal ion uptake and diffusion. Various plant species and metal salts have been utilized in these in vitro approaches, leading to the synthesis of diverse nanoparticles.[32-35]

For example, gold nanoparticles with decahedral icosahedral forms ranging from 20 to 40 nm have been produced using extracts of *Pelargonium graveolens* (rose geranium).[36] Similarly, the gold nanospheres and the nanotriangles with sizes ranging from 0.05 to 18 µm have been created with the use of *Cymbopogon flexuous* (lemon grass) extracts.[37] Tetra chloroauric acid ($HAuCl_4$) has been reduced using *azadirachta indica* (neem) extract to produce flat gold hexagons and triangles that are between 50 and 100 nm in size. Additionally, *A. indica* juice has been demonstrated to reduce silver nitrate to 5 to 25 nm in size polydisperse spherical nanoparticles. These *in-vitro* approaches harness the plant metabolites to aid in the reduction of metal ions into nanoparticles, such as proteins, alkaloids, phenolic acids, terpenoids, and sugars and guarantee their steadiness. It is thought that these biomolecules' interactions with metal ions are mostly responsible for regulating the size and shape of nanoparticles.[38]

The diverse morphologies of nanoparticles produced using various ions of metal in various plant extracts underscore the potential of this approach for tailored nanoparticle production.[39-41]

Solvent System Based Green Synthesis

The solvent system-based "green" synthesis is integral to various synthesis processes, with water being hailed as an ideal and readily accessible solvent. Sheldon aptly noted that "the best solvent is no solvent, and if a solvent is desirable, then water is ideal".[42] The water, abundant and cost-effective, has been used extensively as a solvent for nanoparticle synthesis since the inception of nanoscience and nanotechnology. Notably, silver and gold nanoparticles have been successfully synthesized using the bifunctional molecule gallic acid in an aqueous solution at normal temperature.[43] Furthermore, the laser ablation technique has been applied to generate gold nanoparticles in an aqueous solution, where the presence of oxygen induces the produced gold nanoparticles' partial oxidation, thereby enhancing their chemical reactivity and growth.[44]

In the realm of "green" synthesis, two major routes have emerged: utilizing water as a solvent system and harnessing natural sources or extracts as primary components. Both approaches have been extensively explored in the literature, aiming to provide researchers with insights into "Green" synthesis techniques, the significance of hazardous and non-hazardous solvents or components, and the application of naturally occurring renewable resources. Notable instances within this developing field include ionic liquids (ILs) and supercritical fluids.

Ionic liquids (ILs), often called "room temperature ionic liquids," are made up of ions that have melting points less than 100°C. These ions have been used to create a variety of metal nanoparticles, including Au, Ag, Al, Te, Ru, Ir, and Pt.[45-48] ILs exhibit versatility because they can serve both as, reductants and protective agents, thereby simplifying the nanoparticle synthesis process. The component ions of these ILs might exhibit either hydrophilic or hydrophobic characteristics. For example, 1-butyl-3-methyl imidazolium hexafluorophosphate (PF6) is hydrophobic, but its hydrophilic analog is tetrafluoroborate (BF4). Both kinds can act as catalysts.[47,49–52] Comparative studies have indicated that ILs can yield smaller-sized nanoparticles with superior dispersity compared to conventional solvents.[53-54] Additionally, ILs have found applications in electrochemical methods for nanoparticle synthesis, offering advantages such as the absence of mechanical stirring.[55] As stabilizing agents, thiol-functionalized ionic liquids (TFILs) have been used to produce crystalline nanoparticles with small sizes.[56] Moreover, ILs have been instrumental in developing hydrogenation processes using reusable biphasic catalytic devices.[57]

The advantages of employing ILs over conventional solvents include their ability to dissolve various gases, polar organic molecules, and metal catalysts, along with their broad operating temperature range and tunable solubility properties. Nevertheless, concerns regarding the biodegradability of ILs have spurred efforts to develop potentially benign ILs with enhanced biodegradability.[58-61]

Similarly, when temperatures and pressures above their critical points are reached, common solvents can transform into supercritical fluids. Solvent characteristics at supercritical temperatures undergo significant alterations, offering unique advantages for various reactions. Carbon dioxide, owing to its non-hazardous and inert nature, is a commonly used supercritical fluid.[62-63] Additionally, supercritical water has shown promise as a solvent system for nanoparticle synthesis thanks to its distinctive properties.[64] Noteworthy examples include the nanoparticle production of copper and silver in supercritical carbon dioxide,[65] and the application of supercritical water to produce nanoparticles made of tungsten oxide.[66,67]

Challenges in Green Synthesis

Notwithstanding the benefits of green synthesis, multiple difficulties need to be addressed to optimize the process and ensure the reproducibility and scalability of nanoparticle production. Key challenges include:

Controlled synthesis

Achieving precise control over the size, shape, and composition of nanoparticles continues to be difficult due to biological systems' complexity reducing agents and reaction conditions.

Stability and agglomeration

Green-synthesized nanoparticles are prone to agglomeration and instability, affecting their properties and applications. Strategies to improve stability and prevent aggregation are essential.

Mechanistic understanding

The mechanisms underlying green synthesis reactions are not fully understood, hindering the rational design and optimization of synthesis protocols.

Scale-up and standardization

Transitioning from laboratory-scale synthesis to industrial-scale production requires robust and scalable synthesis protocols and quality control measures.[68]

Evaluation of Green Synthesized Nanoparticles

Accurate characterization of green-synthesized nanoparticles is paramount for comprehending their properties and refining synthesis protocols. Various analytical techniques are employed for characterization, including one often used technique to monitor the formation is UV-vis spectroscopy of nanoparticles based on their plasmonic resonance properties.[69] High-resolution images of nanoparticles are provided by transmission electron microscopy (TEM), which makes it easier to see their morphology, size, and shape.[70] The crystalline structure and phase composition of nanoparticles can be revealed *via* X-ray diffraction (XRD) investigation.[71] By measuring the hydrodynamic size and dispersity of nanoparticles in solution, dynamic light scattering (DLS) provides information about the stability and aggregation behavior of the particles.[72] The examination of fourier transform infrared spectroscopy (FTIR) provides insight into the functional groups found in biomolecules that are involved in the synthesis and stabilization of nanoparticles.[73]

Applications of Green Synthesized Nanoparticles in Pharmaceuticals

The nanoparticles made *via* green synthesis hold significant promise for numerous medicinal uses because of their special qualities and eco-friendly production methods.[74] One prominent application is in drug delivery systems, where the use of nanoparticles can improve the solubility, stability, and bioavailability of the drugs, leading to improved therapeutic efficacy.[75] Additionally, green-synthesized nanoparticles can serve as vehicles for the delivery of certain drugs, enabling precise delivery of therapeutic agents to specific tissues or cells, thus minimizing systemic side effects.[76]

Furthermore, these nanoparticles can be utilized as antimicrobial agents, offering an alternative approach to combating drug-resistant bacteria and fungi.[77] Their inherent antimicrobial properties, combined with their biocompatibility, make them suitable candidates for the development of novel antimicrobial formulations.[78] Green-synthesized nanoparticles have demonstrated efficacy against a variety of pathogens, making them useful for treating a range of infectious illnesses.[79]

In addition to drug delivery and antimicrobial applications, green-synthesized nanoparticles are also employed in diagnostic imaging and sensing.[80] By functionalizing nanoparticles with specific ligands or biomolecules, they can selectively target the disease biomarkers, making it possible to identify and imaging of diseased tissues with high sensitivity and specificity.[81] This talent has the potential for early illness diagnosis and monitoring, leading to better patient outcomes .[82]

Furthermore, nanoparticles made using green synthesis have been investigated for their potential role in cancer therapy, particularly in combination with other therapeutic modalities such as radiation therapy or photodynamic therapy.[83] These nanoparticles can enhance the effectiveness of cancer treatment by sensitizing tumor cells to radiation or light-based therapies, thereby improving tumor eradication while limiting harm to the healthy tissues in the vicinity.[84]

Overall, the use of green-synthesized nanoparticles in pharmaceuticals is diverse and multifaceted, spanning drug delivery, antimicrobial therapy, diagnostic imaging, and cancer treatment. The ongoing investigation and creativity in this area hold the capacity to transform drug development and the provision of healthcare, offering sustainable, effective solutions to pressing medical challenges.

Green-synthesized metal nanoparticles find applications in other fields, including:

Catalysis

Metal nanoparticles serve as efficient catalysts for organic transformations, hydrogenation reactions, and environmental remediation processes.

Environmental remediation

Metal nanoparticles are used for pollutant degradation, treatment of wastewater and extraction of heavy metals from hazardous areas.

Electronics and optoelectronics

Green-synthesized nanoparticles are incorporated into sensors, conductive inks, and optoelectronic devices for applications in renewable energy and electronics.[85]

Future Perspectives

The area of environmentally friendly metal nanoparticle production is poised for significant growth and innovation. Future research directions include:

Advanced characterization techniques

Developments *in-situ* and operando characterization techniques will provide deeper insights into the nucleation, growth, and stability of green-synthesized nanoparticles.[86]

Computational modeling

Computational modeling and simulation approaches will aid in understanding the underlying mechanisms of green synthesis reactions and predicting nanoparticle properties.[87]

Multifunctional nanoparticles

Designing multifunctional nanoparticles with tailored properties for specific applications, such as theragnostics and environmental sensing, holds great potential.[88]

Industrial translation

Efforts to scale up green synthesis methods and integrate them into industrial processes will facilitate the commercialization of green-synthesized nanoparticles.[89-92]

CONCLUSION

An environmentally responsible and sustainable method of producing nanoparticles is by green synthesis of metal nanoparticles. Despite existing challenges, ongoing research efforts aim to go beyond these barriers and unlock the entire capacity of green-synthesized nanoparticles for many uses. Nanoparticles find myriad applications in the fields of medicine and pharmaceuticals, serving as drug delivery systems, enhancing radiation or proton therapy as radiosensitizers, facilitating bioimaging, and acting as bactericides or fungicides. By addressing key challenges, advancing characterization techniques, and exploring novel pharmaceutical applications, the field is poised to make significant contributions to nanotechnology and sustainable development.

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