GREEN-SYNTHESIZED METALLIC NANOPARTICLES AS NEXT-GENERATION DRUG CARRIERS: A COMPREHENSIVE REVIEW

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ABSTRACT

The green synthesis of metallic nanoparticles (MNPs) has emerged as a sustainable and eco-friendly approach in the field of nanomedicine, providing significant advantages over conventional chemical and physical synthesis methods. This review analyses the potential of green-synthesized MNPs as next-generation drug carriers, with a focus on their biocompatibility, stability, and targeted drug delivery potentialities. Utilising various biological sources employed in green synthesis, characterization techniques, and the mechanisms of drug loading and release. Furthermore, the recent biomedical applications are highlighted, including cancer therapy, antimicrobial treatments, and gene delivery, while addressing challenges related to toxicity, scalability, and regulatory concerns. The review concludes with projections for future advancements in green nanotechnology aimed at improving therapeutic outcomes.

Key words: *Green synthesis; Metallic nanoparticles (MNPs); Drug delivery; Biocompatibility; Targeted drug release; Nanomedicine; Eco-friendly nanotechnology; Biomedical applications.*

INTRODUCTION

Metallic nanoparticles (MNPs) have gained significant attention in the field of nanomedicine due to their unique physicochemical properties, including high surface-to-volume ratio, tunable optical and magnetic properties, and enhanced reactivity [4][1][7][6] [5]. These features make MNPs highly effective as drug carriers, enabling targeted and controlled drug release. However, conventional synthesis methods involve toxic chemicals and energy-consuming processes, raising environmental and biocompatibility concerns [2,3] [8,9].Green synthesis offers a sustainable alternative by utilizing biological sources such as plants, bacteria, fungi, and algae for nanoparticle production. This approach reduces toxic byproducts, enhances biocompatibility, and aligns with the principles of green chemistry [10 - 14]. The use of biomolecules from natural sources acts as reducing and stabilizing agents, leading to the formation of nanoparticles with improved stability and functional properties [15 - 19].

The increasing demand for safer and more efficient drug delivery systems has driven research into green-synthesized MNPs. Recent studies have demonstrated their potential in various biomedical applications, including cancer therapy and antimicrobial treatments. Research highlights their use in improving drug bioavailability, reducing toxicity in system, and increasing targeted drug delivery mechanisms [1][4 - 7]. This review aims to provide a comprehensive analysis of green synthesis techniques, characterization methods, and biomedical applications of MNPs in drug delivery. By exploring recent advancements and addressing existing challenges, this work highlights the potential of green nanotechnology in revolutionizing therapeutic strategies. MNPs play a crucial role in modern drug delivery by offering site-specific and sustained drug release, minimizing toxicity in system, and improving therapeutic efficacy. Their nano-size enables penetration through biological barriers, including the blood-brain barrier, facilitating the delivery of drugs to previously inaccessible sites [10 - 14]. Additionally, MNPs can be engineered for multi-functional applications, such as simultaneous imaging and therapy (theranostics), enhancing disease diagnosis and treatment [15 - 19].

Limitations of Conventional Synthesis Methods: Despite their advantages, conventional synthesis methods for MNPs present different drawbacks that limit their biomedical applications. These methods typically involve chemical and physical approaches that require toxic reducing agents, stabilizers, and high-energy inputs, leading to environmental and biological concerns [11,12]. Some of the key limitations include: i) Toxicity of Chemical Reagents**:** These methods often involve perilous substances such as sodium borohydride, hydrazine, and organic solvents, which pose risks to human health and the environment [5 ,7].ii) High Energy Consumption: The Physical synthesis techniques, like laser ablation, thermal decomposition, and sputtering, require very high temperatures, pressures, or laser intensities, making them energy-consuming and costly [4,1].iii) Poor Biocompatibility: MNPs synthesized using regular methods often require additional surface modifications to improve their stability, dispersibility, and biocompatibility, adding difficulty to the production process [20 ,9].iv) Low Yield and Scalability Issues: Many traditional synthesis processes produce low yields of nanoparticles with inconsistent size and shape, making large-scale production challenging [3 ,8].v) Environmental Impact: The by-products from chemical synthesis are toxic and can lead to environmental pollution, necessitating stricter waste management and regulatory controls [10, 13].

Importance of Green Synthesis as Eco- Friendly Alternative: Green synthesis of MNPs has become evident as a promising alternative to conventional methods, aligning with green chemistry principles to minimize environmental and biological hazards. Unlike chemical and physical synthesis, green synthesis use biological entities such as plant extracts, microorganisms, and biomolecules, which act as natural reducing and stabilizing agents, eliminating the need for toxic chemicals [1] [4 , 5]. This approach offers many advantages: i) the use of unsafe chemicals, reducing environmental pollution and promoting sustainable nanoparticle production [6 , 7],use of natural capping agents enhances the biocompatibility of MNPs, making them more suitable for

biomedical applications [2 - 3],synthesis occurs under mild reaction conditions, requiring lower temperatures and energy inputs, making it a cost-effective and scalable process [8 - 9]. Biomolecules in plant extracts and microbial cultures can provide additional functional groups on the nanoparticle surface, enhancing their drug-loading capacity and stability [10,13]. Plant-based synthesis leverages renewable resources, contributing to a circular economy and sustainable healthcare solutions [15-16].

PRINCIPLES OF GREEN SYNTHESIS

Eco friendly green synthesis refers to the production of metallic nanoparticles using biological entities such as plants, microorganisms, and biomolecules. By following the principles of green chemistry, emphasizing the use of non-toxic reagents, energy-efficient processes, and sustainable resources [10][11][5].

The Sources of Synthesis are **i) Phytochemicals as Reducing Agents**: Plant extracts contain various bioactive compounds, including flavonoids, alkaloids, polyphenols, and terpenoids, which perform as natural reducing and stabilizing agents in nanoparticle synthesis[1,2]. These phytochemicals pave the way for the conversion of metal ions into stable nanoparticles while imparting additional therapeutic properties.**ii) Microorganisms: Bacteria, Fungi, Algae**: Microbial synthesis of MNPs involves bacteria, fungi, and algae, which possess enzymes and metabolites capable of reducing metal ions into nanoparticles. Examples include *Chlorella vulgaris*, *Aspergillusniger*, and *Bacillus subtilis* [3][8][13].**iii) Mechanism of Nanoparticle Formation:** The biological reduction of metal ions occurs through enzymatic and non-enzymatic processes, where biomolecules donate electrons to metal ions, leading to nanoparticle formation. This self-assembly process ensures controlled size and morphology of the nanoparticles [4,9].

Table 1: Comparison of Green Synthesis Methods

Biological Source	**Synthesis Conditions**	**Yield**	**Particle Size**	**Reference**
Ocimum sanctum (Tulsi) Leaf Extract	pH 7, Room Temperature	Moderate	20-50 nm	[1]
Funlus niger)	28°C, pH 6	High	15-40 nm	[9]
Algae (Chlorel	Sunlight Exposure	Moderate	5-20 nm	[13]
plant extracts rich in biomolecules such as proteins, alkaloids, flavonoids, reducing sugars, and polyphenols.	pH 4-8, 60-80°C	Variable	10-100 nm	[7]
Fungi (Aspergillus niger)	28°C, pH 6	High	15-50 nm	[8]

Various leaves and flowers	Room Temperature, pH 7	Moderate	20-80 nm	[10]
Microalgae and Fungi)	Controlled pH and Temperature	High	10-100 nm	[12]
Microorganisms (Bacteria, Fungi)	Controlled pH and Temperature	High	10-50 nm	[14]
Marine Organisms	Sunlight Exposure, pH 7	High	20-70 nm	[16]
Phytochemicals (Various Plant Extracts)	pH 4-8 controlled Temperature	Variable	10-80 nm	[18]

TECHNIQUES USED FOR CHARACTERIZATION

Inorder to confirm the stability, biocompatibility and efficiency of the green-synthesized MNPs, suitable characterization is needed for their completion of the task. The following analytical techniques are used to determine the physicochemical properties of MNPs:

- The optical properties are analyzed and confirmed nanoparticle formation by using the absorption spectra technique and detecting surface plasmon resonance (SPR) [10][11]. The model UV-Vis graph for Zinc, Silver and Gold green synthesized MNPs. [Fig 1]

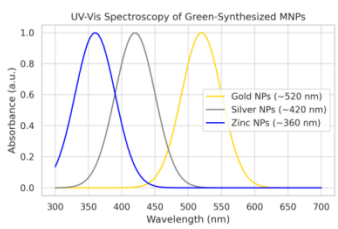

Fig.1

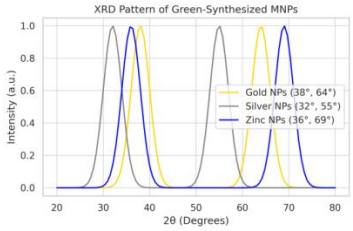

Fig.2

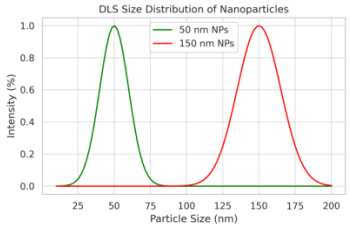

Fig.3

- In order to confirm the crystalline structure, phase identification, and average particle size of green synthesised MNPs XRD technique is used [4][13].The ideal XRD pattern of green synthesized MNPs is shown in [Fig.2].
- To identify the existing functional groups and biomolecules in nanoparticle capping and stabilization FTIR technique is used[15][17].
- TEM technique offers high-resolution images to determine particle morphology, size, and dispersion [6][3].

- Dynamic Light Scattering (DLS) is used **t**o Measure the hydrodynamic size and zeta potential, providing insights into nanoparticle stability and surface charge [1][7]. The model graph compatible with target drug delivery is shown in the Fig.3.

Table 2:Characterisation Techniques

Technique	**Parameter Measured**	**Key Observations**	**Reference**
UV-Vis Spectroscopy	Surface Plasmon Resonance	SPR peak at ~420 nm for AgNPs	[1]
X-Ray Diffraction (XRD)	Crystalline structure	Face-centered cubic (FCC) phase identified	[4]
Fourier Transform Infrared (FTIR)	Functional Groups Inv C=O, and C-H functional groups detected	**O-H Stretching:** Around 3200-3600 cm^{-1} indicating hydroxyl groups from phenols or alcohols acting as reducing and stabilizing agents. **C=O Stretching:** Around 1600-1700 cm^{-1}, corresponding to carbonyl groups from proteins or flavonoids involved in nanoparticle capping. **N-H Bending:** Around 1500-1600 cm^{-1}, associated with amide groups from proteins or peptides contributing to stabilization. **C-H Stretching:** Around 2800-3000 cm^{-1}, indicating the presence of alkane groups from plant metabolites. **C-O-C Stretching:** Around 1000-1300 cm^{-1}, showing the presence of ethers or esters from polysaccharides involved in nanoparticle formation.	[5] [7]
Transmission Electron Microscopy (TEM)	Particle Morphology and Size of	Particle size varying from 10 – 50 nm	[6]

	nanoparticles, 20-50 nm		
Dynamic Light Scattering (DLS)	Hydrodynamic Size, Zeta Potential	Narrow size, high stability	[2]

Importance of stability and surface Modification: Ensuring the stability of green-synthesized MNPs is crucial for their biomedical applications. Stability is influenced by factors such as:

- **Surface Charge and Zeta Potential:** Higher zeta potential values indicate better colloidal stability, preventing aggregation [2,9].
- **Capping Agents and Functionalisation:** Biological molecules (proteins, polysaccharides, flavonoids) act as stabilizing agents, enhancing dispersibility and bioactivity [5,18].
- **Storage Conditions:** Temperature, pH, and ionic strength impact nanoparticle longevity and performance [8 ,19].

In drug delivery application surface modification need to be optimised. Functionalisation with targeting ligands (e.g., antibodies, peptides) improves specificity, while polymer coatings enhance drug loading and release profiles [16,14].

Strategies for drug encapsulation: Encapsulation of drugs within metallic nanoparticles (MNPs) enhances their stability, bioavailability, and therapeutic efficacy. Several strategies can be employed to encapsulate drugs within MNPs, each with distinct benefits:

- **Physical Encapsulation:** This involves loading the drug by physical adsorption onto the nanoparticle surface, which is often achieved through simple electrostatic interactions or mixing. This approach is generally easy and cost-effective but can lead to low drug loading efficiency [5,8].
- **Chemical Encapsulation:** Drugs can be covalently bonded to MNPs, ensuring a more stable and controlled release profile. This strategy is particularly useful when a sustained release is required [4-5].
- **Polymeric Coating:** The use of polymers as a coating for MNPs can encapsulate hydrophobic drugs, enhancing solubility and preventing premature drug release [6,15]. These coatings can also enable the incorporation of functional groups that improve the nanoparticle's drug-loading capacity.
- **Liposome-Based Encapsulation:** Liposomes can serve as carriers for MNPs, improving cellular uptake and drug delivery efficiency. Liposome-based MNPs are especially useful for the delivery of hydrophilic drugs [10,11].

Regulated and targeted Drug release: Regulated and targeted drug delivery is a vital characteristic of MNPs, enabling drugs to be delivered precisely where they are needed, improving therapeutic efficacy while reducing side effects.

- **Stimuli-Responsive Systems:** MNPs can be designed to respond to various stimuli, such as pH, temperature, or light, enabling controlled drug release at the target site [9,3].
- **pH-Sensitive Systems:** Exploiting the acidic pH of tumor tissues or the lower pH of endosomes and lysosomes can trigger the release of drugs from MNPs in a controlled manner [7,15].
- **Thermal and Enzyme-Responsive Systems:** MNPs that release drugs upon temperature elevation are particularly useful in hyperthermia-based therapies. Enzyme-responsive systems utilize enzymes like proteases to break down nanoparticles at the disease site, facilitating targeted drug release [4,16].
- **Magnetic Targeting:** Magnetic MNPs can be attracted to specific sites by applying an external magnetic field, allowing for spatially controlled drug delivery [10,13].

FACTORS INFLUENCING DRUG DELIVERY EFFICIENCY

Several factors affect the efficiency of drug delivery using MNPs. These include: **i)pH Sensitivity:** Tumor tissues and specific intracellular compartments (like endosomes) exhibit acidic environments, which can trigger drug release from pH-sensitive MNPs [11,7].**ii) Temperature Sensitivity:** MNPs can be engineered to release drugs upon exposure to higher temperatures, which is particularly beneficial in hyperthermic treatment strategies [5,14].**iii) Enzyme Responsiveness:** Specific enzymes present at the disease site (such as proteases in tumors) can trigger the breakdown of nanoparticles and release the encapsulated drug [8,3].**iv) Nanoparticle Size and Surface Charge:** The surface charge and size of MNPs influence their stability, cellular uptake, and release kinetics, which are critical in ensuring efficient drug delivery [2,15].

Cancer Therapy: Targeted Drug delivery Photothermal Therapy: Nanoparticles facilitate precise drug targeting to cancerous tissues, minimizing systemic toxicity. Liposomes, dendrimers, and polymeric nanoparticles are widely used for drug encapsulation. Photothermal therapy (PTT) employs gold nanoparticles (AuNPs) and carbon-based nanomaterials to convert light into heat, selectively destroying cancer cells. Nanocarrier-based drug delivery enhances tumor penetration, improving therapeutic outcomes and patient survival rates.[20-21].

Antimicrobial Applications: Use in Combating Drug - Resistant Bacteria : The rise of multidrug-resistant bacteria necessitates alternative therapeutic strategies. Silver nanoparticles (AgNPs), graphene-based materials, and lipid-based nanocarriers exhibit potent antimicrobial

properties by disrupting bacterial membranes and inhibiting biofilm formation. Additionally, nanoformulations enhance antibiotic delivery, improving efficacy against resistant strains[22-23].

Gene Delivery: Role in Genetic Engineering and CRISPR Applications: Nanocarriers such as lipid nanoparticles (LNPs) and polymeric vectors enhance the delivery of nucleic acids, including CRISPR-Cas9 components. These advancements are revolutionizing gene editing, improving transfection efficiency, and reducing off-target effects. Nanotechnology also enables controlled release mechanisms and targeted intracellular delivery, enhancing gene therapy's precision and effectiveness [24-25].

Anti-inflammatory and wound healing: Enhancing Tissue regeneration: Nanomaterials such as hydrogel-based nanoparticles, cerium oxide (CeO2) NPs, and exosome-mimicking vesicles accelerate wound healing by modulating inflammatory responses and promoting angiogenesis. Additionally, nanotechnology-based dressings provide antibacterial effects, reduce infection risks, and improve healing rates in chronic wounds [26-27].

Table 3: Biomedical applications:

Application	**Drug Delivery System**	**Therapeutic Outcome**	**Toxicity Studies**	**Reference**
Cancer Therapy	Targeted Drug Delivery, Photothermal Therapy	Enhanced tumor penetration and inhibition, Selective destruction of cancer cells	Low systemic toxicity	[20]
Antimicrobial Activity	Silver Nanoparticles (AgNPs)	Broad-spectrum antimicrobial effects, Effective against drug-resistant bacteria	Biocompatibility confirmed	[4] [23]
Anti-inflammatory – Nanoparticles	Modulation of inflammatory responses, Accelerated wound healing, Reduced infection rates	Safe for chronic wound application	Cytotoxicity, Inflammation and oxidative stress	[6][27]
Antiviral Activity	Metal Oxide Nano	Inhibit replication, Enhanced antiviral efficacy	No significant cytotoxicity	[19]

Biosensing	Quantum Dots, Gold Nanoparticles	High sensitivity ay in detecting biomarkers	Non-toxic and biocompatible	[18]
Anti-cancer Therapies	Immuno targeted Nanoshells, Gold Nanoparticles	Integrated cancer imaging, Increased treatment specificity	Minimal off-target effects	[21]
Drug Delivery Systems	Liposomes, Polymeric Nanoparticles	Enhanced bioavailability, Controlled drug eted delivery to specific cells	Improved therapeutic index, Reduced systemic toxicity	[24]

CONCLUSION

Nanotechnology continues to revolutionize biomedicine by enhancing therapeutic precision and efficacy. Future research should focus on clinical translation, safety evaluation, and large-scale manufacturing of nanomedicines to harness their full potential. Green-synthesized metallic nanoparticles (MNPs) present a revolutionary approach in drug delivery systems, offering enhanced biocompatibility, stability, and targeted therapeutic efficacy. By utilizing natural biological sources such as plants, bacteria, fungi, and algae, green synthesis eliminates toxic chemicals, promoting eco-friendly and sustainable nanoparticle production. This review has highlighted the potential of green-synthesized MNPs as next-generation drug carriers, demonstrating their versatility in cancer therapy, antimicrobial treatments, gene delivery, and other biomedical applications. Despite significant progress, challenges such as scalability, reproducibility, and regulatory approval remain barriers to clinical translation. To overcome these challenges, interdisciplinary research is needed to optimize synthesis protocols, enhance characterization techniques, and ensure consistent quality and safety standards. Furthermore, comprehensive in vivo studies and clinical trials are essential to evaluate long-term biocompatibility and therapeutic efficacy.

FUTURE SCOPE

1. **Advanced Functionalization and Targeting:** Future research should focus on functionalizing green-synthesized MNPs with specific ligands for enhanced cellular targeting, enabling personalized medicine approaches.
2. **Multi-Functional Platforms:** Developing multifunctional nanoparticles with combined diagnostic and therapeutic capabilities (theranostics) can revolutionize disease management.

3. **Scaling Up and Commercialization:** Efforts are needed to scale up green synthesis processes for industrial production while maintaining cost-effectiveness and environmental sustainability.
4. **Regulatory and Safety Guidelines:** Establishing standardized regulatory frameworks and safety guidelines will accelerate the clinical translation of green-synthesized MNPs.
5. **Exploring New Biological Sources:** Expanding the use of under-explored biological sources such as marine algae and extremophiles could offer unique properties and functionalities.

The future of green-synthesized MNPs in drug delivery is promising, paving the way for innovative therapeutic strategies with minimal environmental impact. Collaborative efforts between researchers, industry stakeholders, and regulatory bodies will be pivotal in transforming this emerging technology into mainstream medical applications.

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