# Green-Synthesized Nanomaterials for Targeted Drug Delivery Recent Advances, Mechanisms and Translational Challenges

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**Abstract**

Targeted drug delivery systems have revolutionized modern therapeutics by enabling site-specific drug accumulation while minimizing systemic toxicity and adverse effects. However, the clinical translation of many conventional nanocarriers remains limited due to concerns regarding biocompatibility, environmental impact, and manufacturing complexity. Green-synthesized nanomaterials have emerged as promising alternatives, utilizing plant extracts, microorganisms, and naturally derived biomolecules to produce sustainable and biologically compatible nanocarriers. Their unique surface chemistry and bioactive capping agents enhance stability, cellular interactions, and therapeutic performance. Recent advances have expanded the application of green nanocarriers in cancer therapy, brain-targeted delivery, gene and RNA therapeutics, antimicrobial treatment, and theranostic platforms. Their efficacy is governed by complex nano–bio interactions, including passive and active targeting mechanisms, stimuli-responsive drug release, and intracellular trafficking pathways. Surface functionalization and biomimetic engineering have further improved targeting precision and controlled drug release. Despite encouraging preclinical outcomes, significant translational barriers persist. Variability in green synthesis protocols, challenges in large-scale manufacturing, limited long-term safety data, and the absence of standardized regulatory frameworks continue to impede clinical adoption. This review critically discusses the mechanistic principles, recent advances, and translational challenges of green-synthesized nanomaterials for targeted drug delivery. Future integration of artificial intelligence-driven design, personalized nanomedicine, and sustainable pharmaceutical manufacturing may accelerate the development of clinically viable and environmentally responsible nanotherapeutic systems.

**Keywords:** Targeted drug delivery systems, Green-synthesized nanomaterials, Precision nanomedicine, Nano-bio interactions, Clinical translation

## 1. Introduction

The development of targeted drug delivery systems (TDDS) has become a central focus of modern pharmaceutical research owing to their potential to enhance therapeutic efficacy while minimizing systemic toxicity. Conventional drug delivery approaches often suffer from poor bioavailability, rapid drug degradation, non-specific tissue distribution, and dose-limiting adverse effects, resulting in suboptimal clinical outcomes. These limitations are

particularly evident in the treatment of complex diseases such as cancer, neurological disorders, and chronic inflammatory conditions, where precise localization of therapeutics is essential for effective treatment [1].

Nanotechnology has emerged as a transformative platform for overcoming these challenges through the development of nanoscale drug carriers capable of improving drug solubility, circulation time, controlled release, and site-specific delivery. Various nanocarriers, including metallic nanoparticles, polymeric nanoparticles, liposomes, and hybrid nanostructures, have demonstrated significant promise in advancing precision medicine. However, the synthesis of many conventional nanomaterials relies on toxic chemicals, energy-intensive processes, and hazardous solvents, raising concerns regarding environmental sustainability, biological safety, and clinical applicability [2].

In this review, green-synthesized nanomaterials have attracted growing interest as sustainable and biocompatible alternatives. Utilizing plant-derived phytochemicals, microorganisms, and naturally occurring biomolecules as reducing and stabilizing agents, green synthesis enables the production of functional nanocarriers with reduced toxicity and enhanced biological compatibility. Recent studies suggest that these materials possess unique surface characteristics that significantly influence nano–bio interactions, cellular uptake, and targeting efficiency [2,3].

Despite rapid progress, a comprehensive understanding of the mechanistic pathways governing targeted delivery and the translational barriers limiting clinical adoption remains lacking. Therefore, this review critically examines recent advances in green-synthesized nanomaterials for targeted drug delivery, with particular emphasis on their mechanistic foundations, therapeutic applications, and key translational challenges.

## 2. Green Nanomaterials: Beyond Sustainable Synthesis

Green-synthesized nanoparticles have emerged as a promising class of nanocarriers that integrate environmental sustainability with advanced biological functionality. Unlike conventionally synthesized nanoparticles, green mediated synthesis employes plant-derived phytochemicals, microbial metabolites, enzymes, proteins, and other naturally occurring biomolecules as reducing and stabilizing agents. This approach not only minimizes environmental impact but also imparts distinctive physicochemical and biological properties that are highly advantageous for targeted drug delivery [4]. Phytochemicals such as flavonoids, polyphenols, terpenoids, alkaloids, and polysaccharides remain associated with the nanoparticle surface, influencing particle stability, dispersibility, drug-loading capacity, and biological interactions. These naturally functionalized surfaces can enhance cellular recognition, improve biocompatibility, and reduce immunogenic responses compared with conventionally synthesized nanomaterials [5].

Green nanomaterials, including metallic, polymeric, lipid-based, and hybrid nanoparticles, have demonstrated significant potential for drug encapsulation, controlled release, and targeted therapy. Their naturally functionalized surfaces enhance nano–bio interactions, improve circulation stability, and promote site-specific accumulation, resulting in improved therapeutic efficacy and reduced off-target toxicity. In addition, emerging nanocarriers such as Covalent Organic Frameworks (COFs) offer unique advantages owing to their high porosity, tunable architecture, and exceptional drug-loading capacity, further expanding the scope of targeted drug delivery [6,7].

Importantly, the significance of green-synthesized nanoparticles extends far beyond their environmentally benign production. The bioactive surface functionalities imparted during green synthesis can profoundly influence nano–bio interactions, including protein corona formation, cellular internalization, intracellular trafficking, and controlled drug release. These unique interfacial characteristics not only enhance biocompatibility and targeting efficiency but also play a critical role in determining therapeutic outcomes. Therefore, elucidating the interplay between green

synthesis-derived surface chemistry and biological performance is essential for the rational design of next-generation nanocarriers and for bridging the gap between laboratory innovation and clinical translation in precision nanomedicine.

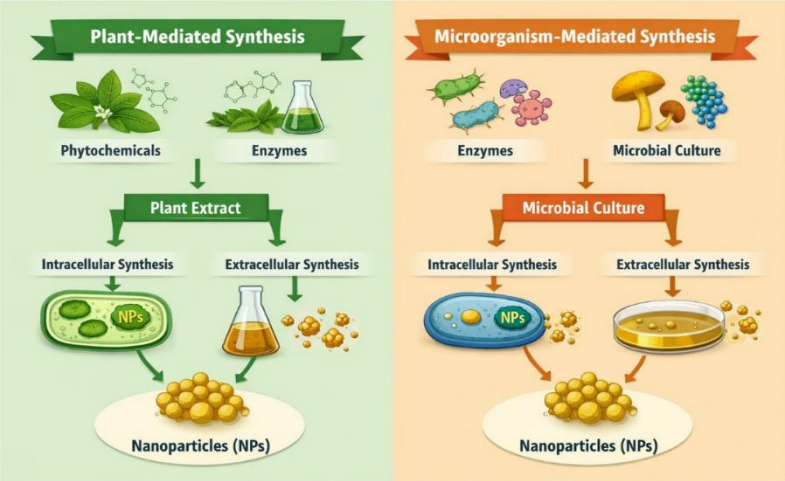


**Figure 1**: Plant-Mediated and Microorganism-Mediated Synthesis of Nanoparticles and their Role in Generating Biologically Functionalized Nanocarriers [7].

**Table 1:** Green-Synthesized Nanomaterials and their Drug Delivery Applications [4, 5, 6, 7, 8]

| Green Nanomaterial | Biological Source | Key Surface Functionalities | Drug Delivery Advantages | Representative Applications |
|---|---|---|---|---|
| **Gold Nanoparticles (AuNPs)** | Plant extracts, fungi | Polyphenols, flavonoids | High biocompatibility, facile surface functionalization, photothermal responsiveness | Targeted cancer therapy, imaging |
| **Silver Nanoparticles (AgNPs)** | Plant extracts, bacteria | Phenolics, proteins | Antimicrobial activity, controlled drug release | Antimicrobial and anticancer delivery |
| **Iron Oxide Nanoparticles (IONPs)** | Bacteria, plant extracts | Polysaccharides, proteins | Magnetic targeting, enhanced cellular uptake | Targeted therapy and diagnostic imaging |
| **Polymeric Nanoparticles** | Natural polymers (chitosan, alginate) | Hydroxyl, amino, carboxyl groups | Biodegradability, sustained drug release | Gene delivery, controlled drug delivery |
| **Lipid-Based Nanocarriers** | Natural lipids and phospholipids | Biocompatible lipid interfaces | Improved drug solubility and bioavailability | Cancer and CNS drug delivery |
| **Hybrid Nanoparticles** | Plant-derived biomolecules with inorganic cores | Multifunctional bioactive coatings | Enhanced stability and targeting efficiency | Multifunctional theranostics |
| **Covalent Organic Frameworks (COFs)** | Bio-derived organic building blocks | Tunable porous framework, functional groups | High drug-loading capacity, stimuli-responsive release, surface modification flexibility | Precision drug delivery, cancer therapy, gene delivery |

## 3. Mechanistic Framework Governing Targeted Delivery

The therapeutic efficacy of nanocarrier-based drug delivery systems is governed by a series of complex interactions occurring at the nano–bio interface. Following systemic administration, green-synthesized nanoparticles encounter diverse biological environments that influence their circulation, biodistribution, cellular uptake, and intracellular

fate. Understanding these mechanistic processes is essential for optimizing targeted drug delivery and improving therapeutic outcomes [7, 8].

The first critical event is the formation of nano-bio interfaces, where nanoparticles encounter biological fluids rich in proteins, lipids and other biomolecules. Physicochemical characteristics such as particle size, morphology, surface charge and surface chemistry govern these interactions initially. The naturally occurring biomolecular coatings associated with green-synthesized nanoparticles can enhance colloidal stability, improve biocompatibility, and reduce undesirable immune responses [8,9].

Upon systemic administration, nanoparticles rapidly absorb plasma proteins, forming a protein corona that alters their biological identity. The composition of this corona influences circulation time, immune clearance, cellular recognition and targeting efficiency. Green-synthesized surface functionalities, such as phytochemicals or biomolecules may modulate protein adsorption patterns, potentially reducing opsonization and prolonging systemic circulation compared with conventional nanocarriers [10].

Following protein corona formation, nanoparticle biodistribution is influenced by factors such as size, surface chemistry, and circulation persistence, as well as interactions with biological clearance mechanisms. Optimizing biodistribution is essential for maximizing drug accumulation at the pathological sites with limited systemic exposure. In contrary, the biofunctionalized surfaces of green-synthesized nanoparticles may improve stability in biological environments and reduce unintended interactions with healthy tissues, thereby enhancing targeting efficiency and therapeutic selectivity [10,11].

Target accumulation occurs through two ways- active and passive targeting mechanisms. Passive targeting relies on enhanced permeability and retention (EPR) effect, where the nanoparticles preferentially accumulate in tumor tissues through leaky vasculature. In contrast, active targeting employs incorporating the ligands antibodies, peptides or aptamers to selectivity bind overexpressed cellular receptors, thereby enhancing uptake specificity and therapeutic precision [12].

Following target-site accumulation, nanoparticles are internalized through cellular pathways such as clathrin-mediated endocytosis, caveolae-mediated endocytosis, micropinocytosis and phagocytosis. The predominant uptake mechanism depends on nanoparticle characteristics and cellular environment. Internalized nanocarriers subsequently undergo intracellular trafficking through endosomal and lysosomal compartments, where premature degradation may reduce therapeutic efficacy [10,14].

To overcome intracellular barriers, advanced green nanocarriers employ stimuli-responsive drug release mechanisms triggered by pathological conditions such as acidic pH, elevated glutathione levels, enzyme overexpression, or temperature changes. These triggers facilitate site-specific drug release while minimizing premature leakage. Furthermore, efficient endosomal and lysosomal escape enables cytosolic delivery of therapeutic cargo, enhancing intracellular bioavailability and therapeutic efficacy [13-15].

Collectively, the nano-bio interface, protein corona formation, biodistribution, targeting mechanisms, cellular uptake, intracellular trafficking and stimuli-responsive drug release govern the therapeutic performance of green synthesized nanocarriers. A comprehensive understanding of the processes is crucial for optimizing targeted drug delivery and facilitating the clinical translation of sustainable nanomedicine platforms [7-15].

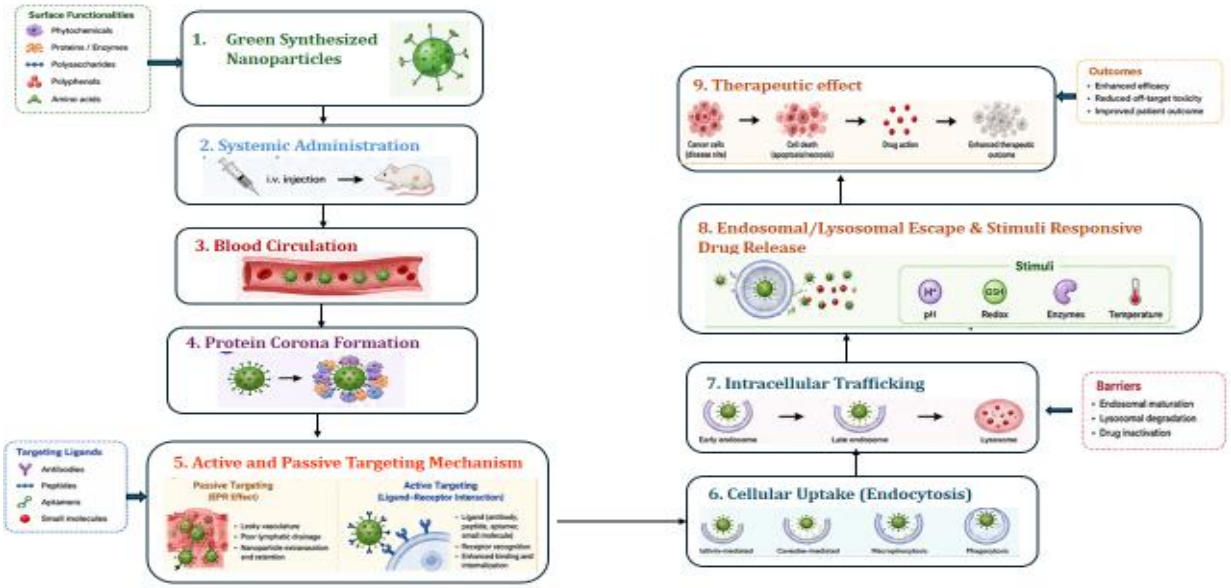


**Figure 2:** Mechanistic Framework Governing Targeted Drug Delivery by Green-Synthesized Nanoparticles

## 4. Recent Advances in Green Synthesized Nanoparticles for Targeted Drug Delivery

Recent advances in green nanotechnology have transformed nanocarriers from simple drug delivery vehicles to multifunctional platforms capable of precise targeting, controlled release and improved therapeutic efficacy. Sustainable synthesis approaches utilizing plant extracts, microorganisms, bioactive molecules and natural polymers have enabled the development of biocompatible nanomaterial with reduction in toxicity and enhancing biological performance.

### 4.1 Metallic and Semiconductor Nanoparticles

Green-synthesized metallic nanoparticles, including gold (AuNPs), silver (AgNPs), and iron oxide nanoparticles (IONPs), continue to attract considerable attention due to their multifunctional properties. Plant and microbe-mediated synthesis improves biocompatibility and reduce the need for toxic reagent. Recent studies have demonstrated the utility of AuNPs for targeted cancer therapy and theranostic applications, while IONPs enable magnetically guided drug delivery and imaging. Furthermore, green-synthesized quantum dots further enable simultaneous drug delivery and bioimaging. However, concerns regarding long-term biodistribution and nanoparticle accumulation remain important challenges [8,10].

### 4.2 Polymeric and Lipid-Based Nanocarriers

Polymeric and lipid-based nanocarriers remain among the most clinically relevant drug delivery systems. Natural polymers such as chitosan, alginate, and gelatin are increasingly utilized to fabricate biodegradable nanoparticles with excellent drug-loading capacity and controlled-release behaviour. Likewise, lipid nanoparticles, including liposomes, solid lipid nanoparticles, and nanostructured lipid carriers, offer enhanced biocompatibility, drug solubility and pharmacokinetic performance. Recent developments focus on ligand-mediated targeting and stimuli-responsive formulations for improved therapeutic precision. Despite their strong translational potential, formulation stability and large-scale manufacturing remain significant challenges [16,17].

### 4.3 Bio-MOFs, COFs, and Zeolites

Porous nanomaterials have emerged as highly promising carriers for precision drug delivery. Green-synthesized biological metal–organic frameworks (bio-MOFs) exhibit exceptional drug-loading capacities, tunable porosity, and biodegradability, enabling efficient therapeutic delivery and controlled release. More recently, covalent organic frameworks (COFs) have emerged as next generation nanocarriers due to their ordered architecture, high surface area, and versatile functionalization capabilities. Their responsiveness to pH, redox conditions, and enzymatic

triggers enables precise spatiotemporal drug release. Zeolites further contribute through sustained-release capabilities. Nevertheless, comprehensive biosafety evaluation and clinical validation remain essential for their translation [1, 6, 18].

### 4.4 Emerging Biomimetic and Multifunctional Nanocarriers

Graphene oxide, exosomes, dendrimers, and polymeric micelles represent emerging multifunctional platforms for targeted drug delivery. Graphene oxide offers exceptional drug-loading capacity and can support photothermal and combination therapies, while exosomes exploit natural cellular communication pathways to improve immune evasion and target recognition. Dendrimers and polymeric micelles further enhance drug solubility, loading efficiency, and controlled release. Despite their promising therapeutic potential, challenges related to biosafety, formulation stability, and large-scale manufacturing continue to limit their clinical translation [2,19,21].

**Table 2:** Comparative Overview of the Recent Advances in Green Synthesized Nanoparticles in Targeted Drug Delivery

| Nanocarriers | Key Advantage | Major Application | Key Limitation |
|---|---|---|---|
| Metallic Nanoparticles (AuNPs, AgNPs, IONPs) | Theranostics, imaging, magnetic targeting | Cancer therapy and diagnostics | Long-term toxicity and accumulation |
| Polymeric Nanoparticles | Biodegradable and controlled release | Drug and gene delivery | Scale-up and reproducibility issues |
| Lipid Nanoparticles | High biocompatibility and clinical relevance | Nucleic acid and anticancer drug delivery | Stability and storage challenges |
| Bio-MOFs | High drug-loading capacity and tunable porosity | Controlled and targeted drug release | Limited clinical validation |
| COFs | Stimuli-responsive and highly tunable structure | Precision nanomedicine and combination therapy | Biosafety and biodegradation concerns |
| Graphene Oxide | High surface area and multifunctionality | Drug delivery and photothermal therapy | Biocompatibility concerns |
| Exosomes | Natural targeting and immune evasion | Gene and biologic delivery | Isolation and large-scale production challenges |
| Dendrimers/Micelles | High drug loading and enhanced solubility | Targeted chemotherapy | Formulation complexity and stability |

## 5. Translational Challenges and Future Perspectives

Despite significant advances in green-synthesized nanomaterials for targeted drug delivery, their clinical translation remains limited due to challenges associated with reproducibility, regulatory approval, and large-scale manufacturing. Unlike conventional nanomaterials synthesized using well-defined chemical processes, green nanomaterials rely on biological precursors such as plant extracts, microbial metabolites, and natural biomolecules whose composition can vary considerably with species, cultivation conditions, extraction methods, and seasonal factors. This variability often leads to batch-to-batch differences in nanoparticle size, morphology, surface

chemistry, and drug-loading efficiency, making reproducibility and quality control difficult to achieve. As regulatory agencies increasingly emphasize Quality-by-Design (QbD) principles, the establishment of standardized synthesis protocols and critical quality attributes is essential for ensuring product consistency and reliability [8,22].

A second challenge relates to the comprehensive characterization of green-synthesized nanomaterials. Residual phytochemicals and biologically derived surface functionalities, while beneficial for biocompatibility and targeting, can influence protein corona formation, biodistribution, cellular uptake, and therapeutic outcomes. However, the precise identity and biological impact of these surface-bound biomolecules are often insufficiently characterized. Regulatory authorities require detailed information regarding nanoparticle composition, degradation behavior, impurity profiles, and long-term safety before clinical approval. The absence of harmonized characterization standards for green nanomedicines therefore represents a significant translational barrier [23].

Scale-up manufacturing remains a major barrier to the clinical translation of green nanomedicines. Although many green synthesis approaches demonstrate promising laboratory-scale performance, maintaining consistent nanoparticle quality, reproducibility, and process control during large-scale production remains challenging. In addition, existing FDA and EMA regulatory frameworks were primarily developed for conventional pharmaceuticals and provide limited guidance for biologically synthesized nanomaterials. Consequently, uncertainties persist regarding characterization standards, safety assessment, quality control, and regulatory approval pathways, highlighting the need for harmonized guidelines and standardized manufacturing protocols [24].

The next phase of green nanomedicine will be driven by the transition from proof-of-concept research to clinically translatable and regulator-ready drug delivery systems. Achieving this goal will require the convergence of sustainable synthesis strategies, advanced material engineering, rigorous quality control, and evidence-based regulatory frameworks. Advanced systems such as bio-MOFs, covalent organic frameworks (COFs), biomimetic nanocarriers, and exosome-inspired delivery vehicles offer unique opportunities for precise targeting, high drug-loading capacity, and stimuli-responsive release [6, 24]. However, their successful implementation will require standardized synthesis protocols, comprehensive safety evaluation, scalable manufacturing strategies, and harmonized regulatory frameworks. The integration of artificial intelligence and machine learning with green synthesis may further accelerate nanoparticle design, process optimization, and prediction of biological performance. Collectively, the convergence of sustainable manufacturing, precision nanomedicine, and regulatory standardization has the potential to transform green-synthesized nanomaterials from promising laboratory constructs into clinically viable next-generation drug delivery platforms [25].

## 6. Conclusion

Green-synthesized nanomaterials are redefining the landscape of targeted drug delivery by integrating therapeutic precision with environmental sustainability. Through advances in metallic nanoparticles, polymeric and lipid-based systems, bio-MOFs, COFs, graphene-derived materials, and biomimetic nanocarriers, these platforms have demonstrated remarkable potential for enhanced targeting, controlled drug release, and reduced systemic toxicity. Despite these achievements, challenges related to reproducibility, characterization, large-scale manufacturing, and regulatory acceptance continue to hinder clinical translation. Addressing these barriers will require interdisciplinary collaboration among materials scientists, pharmaceutical researchers, clinicians, and regulatory agencies. As sustainable nanotechnology converges with precision medicine, green-synthesized nanomaterials are poised to evolve from promising experimental systems into transformative next-generation therapeutics capable of reshaping the future of personalized healthcare.

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