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Green Nanotechnology in Drug Delivery: Sustainable Approaches for the Development of Pharmaceutical Nanocarriers

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ABSTRACT

The rapid expansion of nanotechnology in pharmaceutical sciences has revolutionized drug delivery by enabling controlled release, enhanced solubility, improved bioavailability, and targeted delivery of therapeutic agents. However, conventional physicochemical methods used to fabricate nanocarriers frequently rely on toxic reducing agents, hazardous organic solvents, high energy inputs, and processes that generate substantial chemical waste, raising concerns regarding environmental sustainability, patient safety, and regulatory acceptability. Green nanotechnology has emerged as a transformative paradigm that integrates the twelve principles of green chemistry with nanoscale engineering to produce biocompatible, biodegradable, and eco-friendly pharmaceutical nanocarriers. This review provides a comprehensive analysis of sustainable strategies for the development of nanocarriers, including plant-mediated (phytosynthesis), microbial (bacterial, fungal, algal, and yeast-mediated), and biopolymer-based synthesis routes, along with green solvent systems such as water, ionic liquids, supercritical fluids, and deep eutectic solvents. The classification, formulation strategies, and green fabrication routes of major nanocarrier systems — including liposomes, solid lipid nanoparticles, nanostructured lipid carriers, polymeric nanoparticles (chitosan, PLGA, alginate), dendrimers, metallic and metal-oxide nanoparticles, and cellulose-based nanocarriers — are discussed in detail, supported by comparative tables and schematic figures. The review further addresses characterization techniques, therapeutic applications spanning oncology, antimicrobial therapy, wound healing, and vaccine delivery, along with the toxicological, regulatory, and life-cycle sustainability considerations that currently limit clinical translation. Finally, emerging trends and future research directions toward safe-and-sustainable-by-design nanomedicine are outlined. Collectively, the evidence indicates that green nanotechnology offers a scientifically robust and environmentally responsible pathway for next-generation pharmaceutical nanocarrier development, provided that standardization, scale-up, and regulatory harmonization challenges are systematically addressed.

Keywords: *Green nanotechnology; sustainable drug delivery; pharmaceutical nanocarriers; green synthesis; biopolymer nanoparticles; nanomedicine; green chemistry; eco-friendly nanoparticles*

1. Introduction

Nanotechnology, defined broadly as the design, characterization, and application of materials and devices at the 1-100 nanometre scale, has fundamentally transformed the landscape of modern pharmaceutical sciences. Since Richard Feynman's seminal 1959 lecture 'There's Plenty of Room at the Bottom' first conceptualized the manipulation of matter at atomic and molecular dimensions, nanoscale engineering has evolved into one of the most active and clinically impactful areas of biomedical research [62]. Within drug delivery, nanocarriers such as liposomes, polymeric nanoparticles, solid lipid nanoparticles, dendrimers, and metallic nanoparticles have enabled substantial improvements in the pharmacokinetic and pharmacodynamic profiles of therapeutic agents, including enhanced aqueous solubility, protection from enzymatic and chemical degradation, prolonged circulation time, controlled and sustained release, and the ability to achieve site-specific or receptor-mediated targeting [7, 63].

Despite these advantages, the conventional fabrication of pharmaceutical nanocarriers has historically depended on physical and chemical methods — including chemical reduction, sol-gel processing, high-energy milling, and emulsification-solvent evaporation — that commonly employ hazardous reducing agents such as sodium borohydride and hydrazine, along with volatile organic solvents, surfactants, and stabilizers of questionable biocompatibility [21, 25]. These processes are frequently energy-intensive, generate substantial quantities of toxic by-products, and raise legitimate concerns regarding the environmental fate of nanomaterials, occupational exposure risks, and the biocompatibility of residual chemical contaminants in the final formulation [43, 46]. As global regulatory frameworks and pharmaceutical manufacturers increasingly prioritize environmentally responsible production, the concept of green nanotechnology has gained substantial momentum as a scientifically credible alternative.

Green nanotechnology applies the twelve principles of green chemistry — first articulated by Anastas and Warner in 1998 — to the design and synthesis of nanoscale materials, emphasizing waste prevention, the use of renewable feedstocks, safer solvents, energy efficiency, and inherently safer chemistry [60]. In the specific context of pharmaceutical nanocarrier development, green approaches replace hazardous chemical reagents with biological resources such as plant extracts, microorganisms, and naturally derived biopolymers, which act simultaneously as reducing, capping, and stabilizing agents [1, 3, 25]. This paradigm shift not only mitigates environmental and occupational hazards but has also been repeatedly reported to enhance the biocompatibility, biodegradability, and therapeutic performance of the resulting nanocarriers, owing to the intrinsic bioactivity of the natural capping agents involved [4, 5].

This review aims to provide a comprehensive and critical synthesis of the current state of green nanotechnology as applied to pharmaceutical nanocarrier development. The scope encompasses (i) the fundamental principles underlying green nanotechnology and their alignment with pharmaceutical manufacturing needs; (ii) the major sustainable synthesis strategies, including plant-mediated, microbial, biopolymer-based, and green-solvent-assisted routes; (iii) the classification and green fabrication of specific nanocarrier systems; (iv) characterization approaches used to validate green nanocarriers; (v) therapeutic applications across major disease areas; and (vi) the toxicological, regulatory, and environmental sustainability considerations that continue to shape the field. The review concludes with an outline of emerging trends and future research priorities necessary to enable the clinical and industrial translation of green pharmaceutical nanocarriers.

2. Green Chemistry and Green Nanotechnology: Fundamental Principles

Green chemistry is formally defined as the design of chemical products and processes that reduce or eliminate the generation and use of hazardous substances across the full life cycle of a material. Anastas and Warner's twelve principles — encompassing waste prevention, atom economy, the use of less hazardous chemical syntheses, the design of safer chemicals, the use of safer solvents and auxiliaries, energy efficiency, the use of renewable feedstocks, the reduction of derivatives, catalysis, the design of degradable products, real-time pollution prevention analysis, and inherently safer chemistry for accident prevention — form the conceptual backbone of green nanotechnology (Figure 4) [60].



Figure 1. The twelve principles of green chemistry (Anastas & Warner, 1998) underpinning sustainable pharmaceutical nanocarrier development.

When applied to nanoscale pharmaceutical systems, green nanotechnology can be understood as operating along three complementary axes. The first is green synthesis, which concerns the choice of starting materials, reducing/capping agents, and reaction media used to generate the nanocarrier itself. The second is green processing, which relates to the energy inputs, equipment, and manufacturing conditions (for example, ambient-temperature aqueous synthesis versus high-temperature calcination) used during fabrication and scale-up. The third is green application and end-of-life management, which considers the biodegradability, biocompatibility, and environmental fate of the nanocarrier once it has been administered or has entered waste streams [44, 45].

A defining feature distinguishing green nanotechnology from conventional nanofabrication is the substitution of hazardous chemical reducing agents (e.g., sodium borohydride, hydrazine hydrate, sodium hypophosphite) with biologically derived reducing and stabilizing agents. Phytochemicals such as flavonoids, polyphenols, terpenoids, alkaloids, and proteins present in plant extracts, as well as enzymes and extracellular metabolites secreted by bacteria,

fungi, yeast, and algae, are capable of reducing metal ions and simultaneously capping the resulting nanoparticles to prevent uncontrolled aggregation [4, 13, 51]. This dual reducing-and-stabilizing functionality is central to the mechanism of green nanoparticle synthesis illustrated schematically in Figure 2.

3. Pharmaceutical Nanocarriers: Overview and Classification

Pharmaceutical nanocarriers constitute a structurally diverse family of delivery systems that share the common purpose of encapsulating, protecting, and controllably releasing a therapeutic payload. Nanocarriers are broadly classified according to their core composition into four major categories: lipid-based systems, polymeric systems, metallic and metal-oxide systems, and carbon-based or dendritic systems (Figure 1).

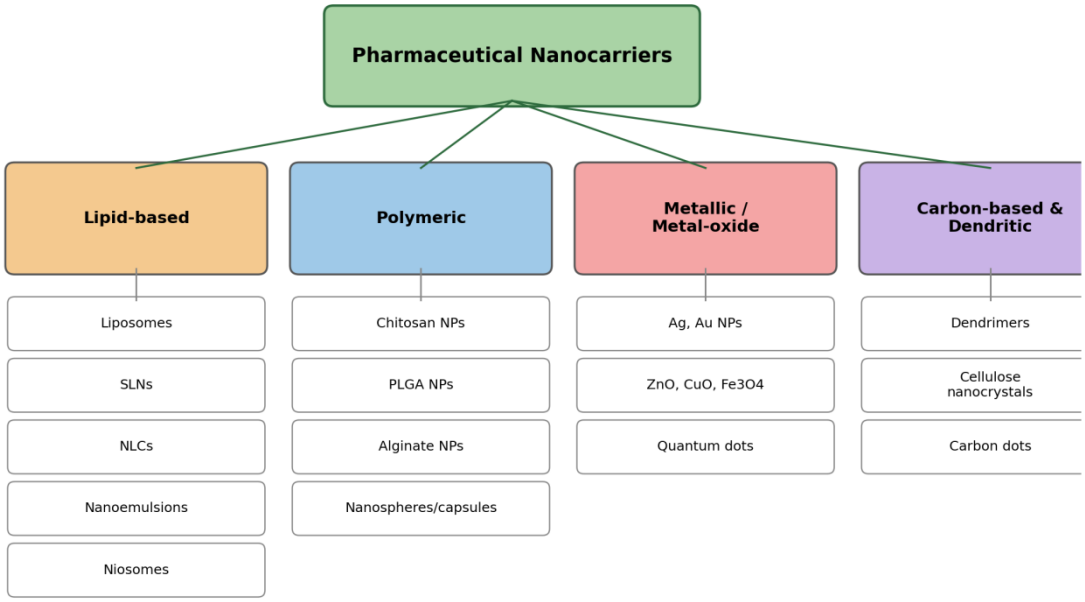


Figure 1. Classification of major pharmaceutical nanocarrier systems.

Lipid-based nanocarriers, including liposomes, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), nanoemulsions, and niosomes, are composed principally of physiologically compatible lipids and are particularly well suited to green formulation because many of their constituent lipids are themselves derived from natural, renewable sources [15, 17]. Polymeric nanocarriers, such as chitosan nanoparticles, poly(lactic-co-glycolic acid) (PLGA) nanoparticles, and alginate nanoparticles, rely on biodegradable natural or synthetic polymers that hydrolyze into non-toxic metabolites [21, 41]. Metallic and metal-oxide nanocarriers, including silver, gold, zinc oxide, copper oxide, and iron oxide nanoparticles, offer unique physicochemical properties such as surface plasmon resonance, magnetic responsiveness, and high surface-area-to-volume ratios that are exploited for drug delivery, imaging, and combined theranostic applications [4, 5, 9]. Carbon-based and dendritic nanocarriers, including dendrimers, cellulose nanocrystals, and carbon dots, provide highly defined, monodisperse architectures amenable to precise surface functionalization [40, 64].

3.1 General Attributes Required of Pharmaceutical Nanocarriers

Irrespective of composition, an effective pharmaceutical nanocarrier must fulfil several core criteria: (i) adequate drug loading capacity and encapsulation efficiency; (ii) colloidal stability during storage and after administration; (iii) a particle size and surface charge compatible with the intended route of administration and biological barrier to be crossed; (iv) controlled or triggered drug release kinetics; (v) biocompatibility and, ideally, biodegradability; and (vi) amenability to reproducible, scalable manufacturing [7, 24]. Green synthesis approaches are increasingly demonstrated to satisfy, and in several respects enhance, these criteria relative to conventional fabrication routes, particularly with regard to biocompatibility and reduced cytotoxicity of residual reagents [5, 31].

4. Sustainable Approaches for Nanocarrier Synthesis

The green synthesis of pharmaceutical nanocarriers can be organized into several overlapping strategies distinguished primarily by the biological or physicochemical source of the reducing/stabilizing agent and the nature of the reaction medium employed. These strategies are summarized comparatively in Table 1 and discussed individually below.

4.1 Plant-Mediated (Phytosynthesis) Approaches

Plant-mediated synthesis, often termed phytosynthesis, is the most extensively investigated green nanofabrication route. Aqueous extracts prepared from leaves, roots, bark, fruit, flowers, and seeds contain a rich repertoire of secondary metabolites — including flavonoids, tannins, saponins, terpenoids, alkaloids, and polyphenolic acids — that reduce metal ions (e.g., Ag+, Au3+, Zn2+, Cu2+) to their corresponding zero-valent or oxide nanoparticles under mild, ambient conditions, while simultaneously adsorbing onto the nanoparticle surface to confer colloidal stability [4, 10, 13]. Species from families such as Asteraceae, along with numerous individual medicinal plants, have been shown to yield nanoparticles with well-defined size, morphology, and enhanced biological activity, including antibacterial, antioxidant, and anticancer effects attributable in part to the residual phytochemical capping layer [11, 14]. Bark-derived extracts, often obtained as valorized waste streams from the timber and food-processing industries, similarly provide a cost-effective and renewable source of reducing biomolecules [12].

4.2 Microbial (Bacterial, Fungal, Yeast, and Algal) Synthesis

Microorganisms represent a second major biological resource for green nanocarrier synthesis. Bacteria synthesize nanoparticles both intracellularly, via enzymatic reduction within the cytoplasm or periplasmic space, and extracellularly, through the secretion of reductase enzymes and metabolites into the surrounding medium; the latter route is generally preferred pharmaceutically because it simplifies downstream purification [51, 56]. Fungi and yeast are particularly attractive biosynthetic platforms owing to their high tolerance to metal ions, ease of large-scale cultivation, and abundant secretion of extracellular enzymes and proteins capable of both reduction and capping, often yielding nanoparticles of superior monodispersity compared with bacterial routes [58, 59, 74]. Algae, spanning brown, red, blue-green, and micro/macro green algal species, contain diverse secondary metabolites and have been increasingly investigated for the intracellular and extracellular biosynthesis of metallic, metal-oxide, and bimetallic nanoparticles with demonstrated antibacterial, antifungal, and anticancer bioactivity [52]. Comparative analyses indicate that bacterial synthesis offers faster growth and greater genetic tractability, whereas fungal synthesis typically confers superior nanoparticle stability and extracellular scalability [56, 57].

4.3 Biopolymer-Based Green Synthesis

Naturally occurring biopolymers — most notably chitosan, alginate, gelatin, pectin, and cellulose — provide an alternative green synthesis platform in which the polymer itself constitutes the nanocarrier matrix rather than merely serving as a capping agent. Chitosan, a cationic polysaccharide derived from crustacean shell waste and recognized as Generally Recognized as Safe (GRAS) by regulatory authorities, is amenable to green nanoparticle fabrication via ionic gelation, polyelectrolyte complexation, microemulsion, and emulsification-solvent diffusion techniques that avoid organic solvents and harsh chemical crosslinkers [19, 23]. Cellulose nanocrystals, derived from renewable plant biomass or agricultural residues, offer high mechanical strength, biodegradability, and a large surface area amenable to drug conjugation [40]. The use of such biopolymers exemplifies the valorization of waste biomass in accordance with circular-economy principles central to green nanotechnology [40, 41].

4.4 Green Solvent Systems

The choice of reaction medium is a further critical determinant of the environmental footprint of nanocarrier synthesis. Conventional organic solvents, many of which are volatile, flammable, and toxic, are increasingly being replaced by water, ionic liquids, supercritical fluids (particularly supercritical carbon dioxide, scCO2), and deep eutectic solvents [32, 34, 37]. Ionic liquids — salts that remain liquid near room temperature — possess negligible vapour pressure, high thermal stability, and tunable solvation properties, making them attractive both as reaction media and, in the form of biocompatible ionic-liquid nanoparticles, as functional drug delivery vehicles in their own right [33, 38]. Supercritical fluid technology enables solvent-free particle size reduction and micronization, circumventing the thermal degradation and residual solvent contamination associated with conventional milling and crystallization processes, and has been applied to the production of nanosized drug particles and lipid nanocarriers alike [36, 45].

4.5 Energy-Efficient Physical Techniques

Complementing the choice of chemical reagents and solvents, green nanotechnology also emphasizes energy-efficient processing methods. Microwave-assisted and ultrasound-assisted synthesis have both been demonstrated to accelerate nanoparticle nucleation and growth while substantially reducing reaction times and overall energy consumption relative to conventional heating, and have been specifically applied to the green fabrication of solid lipid nanoparticles and nanostructured lipid carriers without the use of organic solvents [16]. Mechanochemical and solvent-free grinding methods offer further reductions in waste generation for select nanocarrier classes [25, 39].

4.6 Mechanism of Green Nanocarrier Formation

Across biological synthesis routes, the underlying mechanism follows a broadly conserved sequence: (i) bioactive molecules present in the biological source engage in electron transfer with metal ions or precursor monomers, initiating reduction or polymerization; (ii) nucleation produces initial nanoclusters; (iii) further reduction promotes controlled growth of these nuclei; and (iv) capping biomolecules adsorb onto the nanoparticle surface, arresting growth and conferring long-term colloidal stability through steric and/or electrostatic stabilization. This generalized mechanism is illustrated in Figure 3.

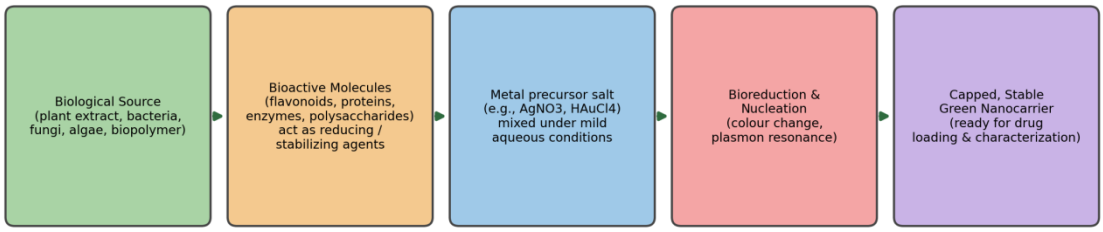


Figure 2. Generalized mechanism of green (biological) synthesis of pharmaceutical nanocarriers.

Table 1. Comparative summary of major green synthesis approaches for pharmaceutical nanocarriers.

Green Synthesis Approach	Representative Sources	Key Advantages	Representative Limitations
Plant-mediated (phytosynthesis)	Leaf, root, bark, fruit, flower extracts	Rapid, low-cost, single-step, wide availability	Batch-to-batch phytochemical variability
Bacterial synthesis	Bacillus, Pseudomonas, Lactobacillus spp.	Genetic tractability, fast growth	Risk of endotoxin contamination
Fungal / yeast synthesis	Aspergillus, Fusarium, Saccharomyces spp.	High extracellular yield, good monodispersity	Longer incubation, culture maintenance
Algal synthesis	Brown, red, blue-green, micro/macro algae	Scalable cultivation, rich metabolite diversity	Species-dependent yield variability
Biopolymer-based	Chitosan, alginate, cellulose, pectin	GRAS status, inherent biodegradability	Batch viscosity/molecular weight variation
Green solvent-assisted	Water, ionic liquids, scCO2, deep eutectic solvents	Low toxicity, recyclable media, solvent-free options	Higher equipment cost (supercritical systems)
Energy-efficient physical methods	Microwave, ultrasound, mechanochemical	Reduced reaction time and energy use	Requires specialized equipment

5. Green Synthesis of Specific Pharmaceutical Nanocarrier Types

5.1 Metallic and Metal-Oxide Nanocarriers

Green-synthesized metallic and metal-oxide nanoparticles — most prominently silver (Ag), gold (Au), zinc oxide (ZnO), copper oxide (CuO), and iron oxide (Fe3O4/Fe2O3) — have been extensively investigated as both direct therapeutic agents and as drug delivery scaffolds. Silver nanoparticles synthesized using plant extracts consistently demonstrate strong antibacterial, antifungal, and antibiofilm activity comparable to or exceeding that of chemically synthesized analogues, attributed to the synergistic action of the metallic core and the adsorbed phytochemical capping layer [5, 10]. Gold nanoparticles, owing to their facile surface functionalization and inherent biocompatibility, are widely explored as carriers for chemotherapeutic and diagnostic agents, and their surface plasmon resonance property enables light-triggered drug release strategies [4, 30]. Zinc oxide and copper oxide nanoparticles generate reactive oxygen species (ROS) that contribute to their antimicrobial and anticancer bioactivity, while iron oxide nanoparticles offer additional magnetic-targeting and imaging capability [4, 9]. Green synthesis of yttrium oxide nanoparticles using plant leaf extracts has similarly demonstrated sustained drug release profiles suitable for controlled delivery applications [2].

5.2 Liposomes and Lipid-Based Nanocarriers

Liposomes, self-assembling phospholipid bilayer vesicles capable of encapsulating both hydrophilic (aqueous core) and hydrophobic (bilayer-embedded) drugs, are inherently amenable to green formulation because their principal building blocks — phospholipids and cholesterol — are naturally derived, biodegradable, and biocompatible [26, 29]. Green hybrid systems combining liposomes with biologically synthesized metallic nanoparticles have been reported, including silver-nanoparticle-loaded liposomes prepared via thin-film hydration coupled with sonication, and gold-nanoparticle-coated doxorubicin liposomes synthesized using plant-derived procyanidins as reducing and stabilizing agents to enable light-controlled drug release [26, 30]. Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs), formulated from physiologically compatible solid and liquid lipids, are

similarly regarded as inherently 'green' materials, and their manufacture is increasingly optimized using microwave- and ultrasound-assisted synthesis to eliminate organic solvents altogether while achieving favourable particle size distributions [15, 16, 18].

5.3 Polymeric Nanoparticles

Chitosan nanoparticles remain among the most widely studied green polymeric nanocarriers, prepared through ionic gelation with polyanions such as sodium tripolyphosphate under entirely aqueous, ambient-temperature conditions. Chitosan-based nanocarriers have demonstrated efficacy in delivering chemotherapeutic agents such as doxorubicin, with the added benefit of overcoming P-glycoprotein-mediated multidrug resistance in cancer cells [20, 22]. Green synthesis routes for chitosan nanoforms and nanocomposites, though still comparatively underexplored relative to plant-mediated metal nanoparticle synthesis, offer opportunities to further reduce the environmental footprint of an already sustainable polymer platform [23]. PLGA nanoparticles, though conventionally prepared using organic solvents such as dichloromethane, are being reformulated using green solvent-diffusion and supercritical fluid techniques to reduce residual solvent toxicity; PLGA-encapsulated paclitaxel formulations have, for example, demonstrated substantially reduced hepatotoxicity relative to conventional Cremophor EL-based formulations [41].

5.4 Dendrimers

Dendrimers are highly branched, monodisperse macromolecules with a well-defined three-dimensional architecture radiating from a central core, offering precisely controllable surface functionality for drug conjugation and targeting ligand attachment [64]. While classical dendrimer synthesis (divergent and convergent methods) often relies on multi-step organic reactions, green modifications employing click chemistry and biodegradable ester or amide linkages have been developed to reduce the number of purification steps and hazardous reagents required, while polyamidoamine (PAMAM) dendrimers conjugated with targeting ligands such as folic acid and hyaluronic acid illustrate the potential for combining green design principles with active tumour targeting [7].

5.5 Cellulose Nanocrystals and Other Carbon-Based Nanocarriers

Cellulose nanocrystals (CNCs), typically extracted from plant biomass or agricultural waste via acid hydrolysis, represent an intrinsically renewable nanocarrier platform with high mechanical strength, tunable surface chemistry, and demonstrated utility in drug delivery, wound healing, and tissue engineering applications [40]. Carbon dots and graphene-based nanomaterials, increasingly synthesized from biomass-derived precursors rather than petrochemical feedstocks, extend the green carbon-based nanocarrier repertoire and are being explored for combined imaging and drug delivery (theranostic) applications [6].

5.6 Niosomes and Nanoemulsions

Niosomes (non-ionic surfactant vesicles) and nanoemulsions represent additional lipid-related nanocarrier classes amenable to green formulation, particularly when formulated using naturally derived surfactants and oils, and are frequently produced via low-energy emulsification methods that avoid high-shear or high-pressure homogenization, further reducing the overall energy footprint of manufacture [25].

Table 2. Representative pharmaceutical nanocarriers, green materials, fabrication routes, and applications.

Nanocarrier Type	**Typical Green Materials / Precursors**	**Common Green Fabrication Route**	**Representative Applications**
Silver / Gold NPs	Plant leaf, flower, bark extracts	Aqueous bioreduction, ambient temperature	Antimicrobial, anticancer, wound healing
Zinc oxide / Copper oxide NPs	Plant extracts, microbial metabolites	Sol-gel with phytochemical reduction	Antibacterial, ROS-mediated anticancer
Iron oxide NPs	Plant extracts (e.g., Cymbopogon citratus)	Co-precipitation with green reducing agent	Magnetic targeting, MRI-guided delivery
Liposomes	Soy/egg phospholipids, cholesterol	Thin-film hydration, sonication	Chemotherapeutics, vaccines
SLNs / NLCs	Natural waxes, triglycerides, phospholipids	Microwave/ultrasound-assisted, solvent-free	Poorly soluble drug delivery, topical delivery
Chitosan nanoparticles	Chitosan (chitin-derived), TPP crosslinker	Ionic gelation (aqueous, ambient)	Gene delivery, oral & mucosal delivery

Nanocarrier Type	Typical Green Materials / Precursors	Common Green Fabrication Route	Representative Applications
PLGA nanoparticles	PLGA, green solvent-diffusion media	Nanoprecipitation / supercritical CO2	Sustained-release chemotherapeutics
Dendrimers (PAMAM)	Biodegradable ester/amide linkers	Click chemistry, divergent green synthesis	Targeted oncology delivery
Cellulose nanocrystals	Plant biomass, agricultural waste	Acid hydrolysis of renewable cellulose	Wound healing, tissue engineering

6. Characterization of Green Pharmaceutical Nanocarriers

Rigorous physicochemical characterization is essential to confirm the successful formation, stability, and pharmaceutical suitability of green-synthesized nanocarriers. UV-visible spectroscopy is routinely used as an initial confirmatory tool for metallic nanoparticles, exploiting characteristic surface plasmon resonance absorption bands (e.g., approximately 400-450 nm for silver nanoparticles) [2, 35]. Dynamic light scattering (DLS) provides hydrodynamic particle size and polydispersity index, while zeta potential measurement offers an indirect assessment of colloidal stability through surface charge quantification [38]. Transmission and scanning electron microscopy (TEM/SEM) provide direct morphological visualization and size confirmation at the nanoscale, while X-ray diffraction (XRD) confirms crystallinity and phase composition [2, 27]. Fourier-transform infrared spectroscopy (FTIR) is particularly valuable in green synthesis studies, as it identifies the specific functional groups of the phytochemical or biomolecular capping agents responsible for nanoparticle reduction and stabilization [9, 27]. Additional techniques, including differential scanning calorimetry (DSC) for thermal behaviour, encapsulation efficiency and in vitro drug release assays, and cytotoxicity/haemocompatibility testing, are employed to establish the pharmaceutical and biological performance of the final formulation prior to preclinical evaluation.

Table 3. Common characterization techniques used for green pharmaceutical nanocarriers.

Technique	Primary Information Obtained
UV-Visible Spectroscopy	Confirmation of nanoparticle formation via plasmon resonance
Dynamic Light Scattering (DLS)	Hydrodynamic particle size, polydispersity index
Zeta Potential Analysis	Surface charge, colloidal stability prediction
TEM / SEM	Particle morphology, size distribution, surface topology
X-ray Diffraction (XRD)	Crystallinity, phase identification
FTIR Spectroscopy	Functional groups of capping/reducing biomolecules
DSC / TGA	Thermal behaviour, drug-carrier interaction, stability
In vitro Release Assay	Drug release kinetics and mechanism
Cytotoxicity / Haemocompatibility Assays	Biological safety profile

7. Applications of Green Pharmaceutical Nanocarriers in Drug Delivery

7.1 Cancer Therapy

Oncology remains the most extensively studied application area for green pharmaceutical nanocarriers. Green-synthesized metal and metal-oxide nanoparticles frequently demonstrate selective cytotoxicity toward cancer cells through mechanisms including ROS generation, induction of apoptosis, DNA damage, and cell-cycle arrest, while exhibiting comparatively reduced toxicity toward normal cells relative to chemically synthesized counterparts [5, 8]. Chitosan and PLGA nanoparticles have been employed for the targeted delivery of chemotherapeutics such as doxorubicin and paclitaxel, exploiting both passive accumulation via the enhanced permeability and retention (EPR) effect and active targeting through ligand conjugation (e.g., folic acid, hyaluronic acid) [20, 41]. Gold-nanoparticle-liposome hybrids further enable light-controlled, spatially and temporally precise drug release for photothermal-chemotherapy combination strategies [30].

7.2 Antimicrobial and Antibiofilm Therapy

Green-synthesized silver and zinc oxide nanoparticles exhibit potent broad-spectrum antibacterial, antifungal, and antibiofilm activity, often attributed to membrane disruption, ROS generation, and interference with microbial protein and nucleic acid function [10, 27]. Chitosan-based nanocarriers additionally enhance antibiotic penetration through bacterial biofilms, offering a promising strategy against multidrug-resistant pathogens, including in the context of tuberculosis therapy [41].

7.3 Wound Healing and Tissue Regeneration

Green metal nanoparticles, particularly silver and copper-based systems, accelerate wound healing through combined antimicrobial action and promotion of angiogenesis and re-epithelialization, while cellulose nanocrystal-based nanocomposite dressings provide additional mechanical support and moisture-retentive properties conducive to tissue regeneration [31, 40].

7.4 Oral, Ocular, and Topical Delivery

Solid lipid nanoparticles and nanostructured lipid carriers formulated via green, solvent-free methods have demonstrated utility in enhancing the oral bioavailability of poorly water-soluble drugs, in sustained ocular drug delivery for conditions such as glaucoma and fungal keratitis, and in topical/transdermal delivery applications owing to their favourable skin permeation and biocompatibility profiles [17, 18, 21].

7.5 Vaccine Delivery and Gene Therapy

Lipid nanoparticles (LNPs), most notably in the context of mRNA-based COVID-19 vaccines, exemplify the translational relevance of green synthesis strategies for the large-scale, efficient manufacture of nucleic-acid delivery vehicles, illustrating the broader applicability of green nanocarrier principles beyond small-molecule drug delivery [41]. Chitosan-based nanoparticles have similarly been explored as non-viral vectors for gene and siRNA delivery, capitalizing on their cationic charge for efficient nucleic acid complexation [24].

7.6 Delivery of Phytochemicals and Natural Bioactives

Green nanocarrier platforms are particularly well suited to the delivery of poorly bioavailable natural bioactive compounds such as curcumin, resveratrol, quercetin, and epigallocatechin gallate, where nanoencapsulation markedly improves aqueous solubility, chemical stability, and cellular uptake, thereby enhancing the translational therapeutic potential of these otherwise pharmacokinetically limited phytochemicals [6].

Table 4. Applications of green pharmaceutical nanocarriers across major therapeutic areas.

Application Area	Representative Green Nanocarrier	Reported Benefit
Cancer therapy	Green Ag/Au NPs, chitosan-DOX NPs	Selective cytotoxicity, reduced systemic toxicity
Antimicrobial therapy	Green AgNPs, ZnO NPs	Broad-spectrum, antibiofilm activity
Wound healing	Green Ag/Cu NPs, cellulose nanocrystals	Faster re-epithelialization, antimicrobial protection
Oral / ocular delivery	SLNs, NLCs (green solvent-free)	Improved bioavailability, sustained release
Vaccines / gene therapy	Lipid nanoparticles, chitosan NPs	Scalable nucleic-acid delivery
Phytochemical delivery	Polymeric & lipid nanocarriers	Enhanced solubility and bioavailability

8. Advantages of Green Nanotechnology over Conventional Approaches

The comparative advantages of green over conventional nanocarrier synthesis span environmental, economic, and pharmaceutical performance dimensions, as summarized qualitatively in Figure 5. Environmentally, green synthesis substantially reduces the use of hazardous solvents and toxic reducing agents, lowers energy consumption through ambient-temperature and microwave/ultrasound-assisted processing, and minimizes the generation of hazardous chemical waste and by-products [1, 43]. Economically, the use of low-cost, renewable, and often waste-derived biological feedstocks (e.g., agricultural residues, bark waste, shellfish processing waste) can substantially reduce raw material costs relative to high-purity chemical reagents [12, 23]. From a pharmaceutical performance perspective, the natural capping biomolecules retained on green-synthesized nanoparticle surfaces frequently confer enhanced biocompatibility, reduced cytotoxicity to healthy tissue, and in several reported cases, additive or synergistic therapeutic activity (e.g., intrinsic antioxidant or antimicrobial effects of the phytochemical corona) that is generally absent in nanoparticles capped with synthetic surfactants [4, 5, 31].

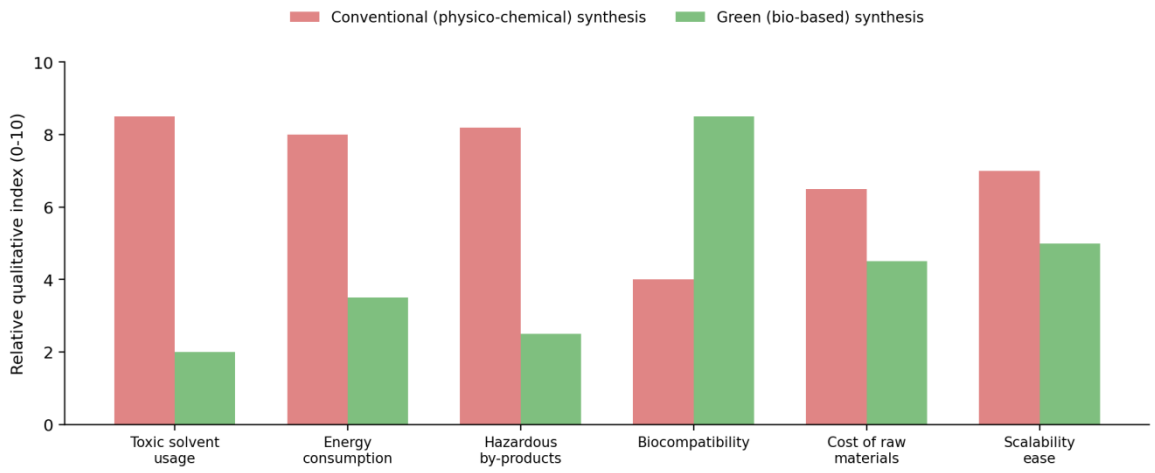


Figure 3. Qualitative comparison of conventional versus green synthesis approaches for pharmaceutical nanocarriers (illustrative summary derived from trends reported in the reviewed literature).

9. Challenges, Toxicity, and Regulatory Considerations

9.1 Standardization and Batch-to-Batch Variability

A principal barrier to the industrial and clinical translation of green nanocarriers is the inherent biological variability of plant extracts and microbial cultures, which can vary substantially with growing conditions, extraction method, harvest season, and microbial strain, leading to batch-to-batch inconsistency in nanoparticle size, morphology, and yield [6, 45]. Establishing standardized extraction protocols, quality control markers, and reproducible culture conditions remains an active area of methodological research.

9.2 Nanotoxicity and Biosafety

It is important to emphasize that green synthesis does not inherently guarantee non-toxicity; nanoparticle safety continues to depend on physicochemical characteristics such as size, shape, surface charge, dosage, and biodistribution, rather than the synthesis route alone [6, 46]. Mechanisms of nanotoxicity — including oxidative stress, mitochondrial dysfunction, inflammatory cytokine release, and interference with cellular signalling pathways — have been documented even for some green-synthesized and FDA-approved nanoformulations, underscoring the necessity of rigorous, case-by-case toxicological evaluation using both in vitro (including advanced three-dimensional culture models) and in vivo assays [49].

9.3 Environmental Fate and Life-Cycle Sustainability

Comparative life-cycle assessment (LCA) studies, applying ISO 14040/44 frameworks, indicate that green synthesis routes can substantially reduce the environmental impact of nanoparticle production relative to conventional co-precipitation and chemical reduction methods; for example, cradle-to-gate LCA of iron oxide nanoparticles synthesized using Cymbopogon citratus extract demonstrated an order-of-magnitude lower normalized environmental impact than the conventional co-precipitation route [48]. Nevertheless, methodological challenges persist in LCA of nanomaterials, including data gaps, toxicity uncertainties, and difficulties in defining appropriate system boundaries, particularly regarding end-of-life fate and long-term ecological transformation of nanomaterials in environmental compartments [44].

9.4 Regulatory Harmonization

Global regulatory frameworks governing nanomedicine, including green nanoformulations, remain fragmented and are widely regarded as still in a developmental stage, particularly with respect to microbially synthesized nanomaterials, where risk-assessment guidance is described in the literature as being in its infancy [45, 47]. Regulatory challenges specific to nanomedicine include the harmonization of characterization standards across jurisdictions, the classification of follow-on ('generic' or 'similar') nanomedicine products, and the translation of nanoparticle-specific pharmacokinetic and toxicological data into risk-based approval pathways [47, 49]. Addressing these gaps will require closer collaboration between academic researchers, industry, and regulatory agencies to develop consensus guidance specific to green-synthesized pharmaceutical nanocarriers.

9.5 Scale-Up and Manufacturing Constraints

While laboratory-scale green synthesis has been extensively demonstrated, the transition to good manufacturing practice (GMP)-compliant, industrial-scale production presents additional challenges, including maintaining sterility and reproducibility in biologically sourced processes, scaling microbial

fermentation or plant extraction economically, and integrating green synthesis steps into existing pharmaceutical manufacturing infrastructure without compromising throughput [47].

10. Future Perspectives

Several converging trends are likely to shape the future trajectory of green nanotechnology in pharmaceutical nanocarrier development. First, the Safe-and-Sustainable-by-Design (SSbD) framework, which integrates safety and environmental sustainability considerations from the earliest stages of material design rather than as a retrospective assessment, is gaining traction as a guiding paradigm for next-generation nanomedicine development [44]. Second, advances in computational and in silico modelling, including machine-learning-assisted prediction of nanoparticle-biomolecule interactions and toxicological outcomes, are expected to accelerate the rational design of green nanocarriers while reducing reliance on extensive empirical screening [46]. Third, the valorization of agricultural, food-processing, and forestry waste streams as feedstocks for green nanocarrier synthesis aligns with circular-economy principles and offers a pathway to further reduce both environmental impact and production costs [12, 40]. Fourth, continued integration of green nanocarriers with precision and personalized medicine approaches, including stimuli-responsive and actively targeted delivery systems, is likely to expand their clinical relevance across oncology, infectious disease, and chronic disease management [8]. Finally, harmonized international regulatory guidance specifically addressing green and biologically synthesized nanomedicines will be essential to enable consistent quality standards and to facilitate clinical translation and market authorization on a global scale [47, 49].

11. Conclusion

Green nanotechnology represents a scientifically robust and increasingly essential paradigm for the sustainable development of pharmaceutical nanocarriers. By replacing hazardous chemical reagents and energy-intensive processes with plant-mediated, microbial, biopolymer-based, and green-solvent-assisted synthesis strategies, this approach substantially reduces the environmental and occupational hazards associated with conventional nanofabrication, while frequently enhancing the biocompatibility and, in several documented cases, the intrinsic therapeutic activity of the resulting nanocarriers. The evidence reviewed here spans the full range of major pharmaceutical nanocarrier classes — lipid-based, polymeric, metallic/metal-oxide, and carbon-based/dendritic systems — and demonstrates consistent applicability of green synthesis principles across oncology, antimicrobial therapy, wound healing, and vaccine delivery applications. Nevertheless, the field continues to face meaningful challenges related to batch-to-batch standardization, comprehensive nanotoxicological characterization, environmental life-cycle assessment, regulatory harmonization, and GMP-compliant scale-up. Addressing these challenges through coordinated research, standardized characterization protocols, and internationally harmonized regulatory frameworks will be essential to fully realize the potential of green nanotechnology as a mainstream, clinically translatable, and environmentally responsible platform for twenty-first-century drug delivery.

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