Journal of Complex Adaptive Systems

Journal Homepage: https://jcas.ut.ac.ir/

Novel Drug Delivery Systems Based on Biological Origins: Nano-Lignin and Cellulose-Derived Nanocarriers for Controlled and Targeted Therapeutics

Ali Abdulkhani[1]✉, **Jaber Hosseinzadeh**[2], **Yahya Hamzeh**[3], **Faezeh Askari**[4], and **Mosayeb Dalvand**[5]

1. Corresponding author, Department of Wood and Cellulose Science and Technology, Faculty of Natural Resources, University of Tehran, Karaj, Iran. Email: abdolkhani@ut.ac.ir
2. Department of Wood and Cellulose Science and Technology, Faculty of Natural Resources, University of Tehran, Karaj, Iran. Email: j.hosseinzade@ut.ac.ir
3. Department of Wood and Cellulose Science and Technology, Faculty of Natural Resources, University of Tehran, Karaj, Iran. Email: hamzeh@ut.ac.ir
4. Department of Wood and Cellulose Science and Technology, Faculty of Natural Resources, University of Tehran, Karaj, Iran. Email: faezeh.askari2010@gmail.com
5. Department of Wood and Cellulose Science and Technology, Faculty of Natural Resources, University of Tehran, Karaj, Iran. Email: m.dalvand@ut.ac.ir

Article Info

Article type:
Research Article

Article history:
Received November 21, 2025
Received in revised form February 19, 2026
Accepted March 22, 2026
Available online March 28, 2026

***Keywords*:**
Antimicrobial Therapy, Biocompatibility, Biomaterials, Nanocellulose, Pharmacokinetics, Wound Healing.

ABSTRACT

Objective: The need for safer, more effective, and more sustainable treatments has increased interest in nanomaterials derived from biological sources. Lignocellulosic biomass, composed mainly of lignin and cellulose, is one renewable source of such carriers. This review critically evaluates nano-lignin and cellulose-derived nanocarriers (cellulose nanocrystals, cellulose nanofibrils, and bacterial nanocellulose) as sustainable drug delivery systems, with emphasis on preparation, functionalization, release behaviour, safety, translational barriers, and future biomedical applications.

Methods: Nano-lignin exhibits antioxidant and ultraviolet-shielding activity and binds hydrophobic drugs through its aromatic network via π–π stacking and hydrogen bonding. Nanocellulose provides mechanical reinforcement, a large surface area, adjustable surface chemistry, and generally good biocompatibility. Preparation methods (antisolvent precipitation, ultrasonication, acid hydrolysis, TEMPO-mediated oxidation) strongly influence particle morphology and drug-loading efficiency. Release is typically diffusion-controlled or stimuli-responsive (pH, redox, enzyme). Biomedical evidence spans cancer therapy, antimicrobial delivery, and wound healing. Hybrid lignin–cellulose systems show complementary mechanical and biological advantages. Translation remains limited by structural heterogeneity, batch-to-batch variation, demanding purification procedures, and the lack of standardized long-term toxicology and pharmacokinetic data.

Results: Nano-lignin and nanocellulose offer distinct yet complementary platforms for controlled and targeted drug delivery. Clinical development is constrained by feedstock variability and the requirements of pharmaceutical standardization, scale-up, and sterilization. Priority research directions include hybrid lignin–cellulose systems, quality-by-design manufacturing, and life-cycle assessment so that clinical performance and environmental cost can be evaluated together. These carriers should be judged on measurable performance and safety, not solely on their renewable origin.

Conclusion: This study contributes to the literature by proposing the integrated SMART framework and illuminating the critical interplay between AI disclosure, greenwashing perceptions, and consumer trust in sustainability communication, offering a foundational theoretical model for future empirical investigations.

Cite this article: Abdulkhani, A., Hosseinzadeh, J., Hamzeh, Y., Askari, F., & Dalvand, M. (2026). Novel Drug Delivery Systems Based on Biological Origins: Nano-Lignin and Cellulose-Derived Nanocarriers for Controlled and Targeted Therapeutics. ***Journal of Complex Adaptive Systems***, *1*(1), 8-38. https://doi.org/10.22059/jcas.2026.418472.1003

Publisher: University of Tehran Press.

DOI: https://doi.org/10.22059/jcas.2026.418472.1003

Introduction

Nanomedicine has expanded the options for targeted drug delivery, improved bioavailability, and reduced systemic exposure in some applications. In this review the term “targeting” is used conservatively: “active targeting” is reserved for systems with demonstrated ligand-mediated uptake, whereas enhanced permeability and retention (EPR)-dependent tumour accumulation is described as passive or site-specific targeting to avoid overstatement. Synthetic polymeric nanoparticles, such as poly(lactic-co-glycolic acid) and polyethylene glycol, and inorganic carriers, including mesoporous silica and gold nanoparticles, have received much of the attention. Their long-term use can nevertheless raise concerns about bioaccumulation, immunogenicity, nonspecific cytotoxicity, and disposal. This has encouraged research on biodegradable carriers derived from renewable biological materials. (Wijaya et al., 2021)

Lignocellulosic biomass comes mainly from agricultural and forestry residues and is one of the most abundant renewable carbon resources. Its main components are cellulose, hemicelluloses, and lignin. Once treated largely as byproducts of pulp, paper, and biofuel production, lignin and cellulose are now processed into functional nanomaterials. Cellulose is a linear homopolymer of β-1,4-linked D-glucose units that gives plant tissue structural strength. Lignin is a cross-linked, amorphous aromatic polymer that contributes recalcitrance, hydrophobicity, and antimicrobial activity to plant cell walls. At the nanoscale, both materials have properties that differ from those of the corresponding bulk materials. (Wijaya et al., 2021; Plackett et al., 2014)

being Lignocellulosic materials are studied as nanocarriers because of their biodegradability, biocompatibility in many tested systems, adjustable morphology, large surface area, and accessible functional groups. These properties can support drug loading, local delivery, and stimulus-dependent release. The hydroxyl groups on nanocellulose allow several chemical modifications, whereas the aromatic rings and phenolic groups in lignin interact with hydrophobic drugs through pi-pi stacking and hydrogen bonding. Because nano-lignin and cellulose-based carriers differ in both chemistry and physical behavior, they are not interchangeable. A direct comparison can therefore help match each carrier to an appropriate formulation. (Wijaya et al., 2021; Plackett et al., 2014)

This review compares nano-lignin to cellulose-based drug carriers and examines how preparation, modification, and functionalization affect carrier performance. It relates drug-loading and release mechanisms to pharmacological behavior, then considers applications in cancer therapy, antimicrobial delivery, wound healing, oral delivery, and tissue engineering. Safety, degradation, manufacturing, and regulatory constraints are discussed alongside the research needed to move these systems beyond laboratory studies.

The aim of this review is to critically evaluate nano-lignin and cellulose-derived nanocarriers as sustainable drug delivery systems, with emphasis on preparation, functionalization, release behaviour, safety, translational barriers and future biomedical applications.

Materials and Methods

This narrative critical review was informed by searches of Scopus, Web of Science, PubMed, and publisher databases. Searches combined terms for lignin nanoparticles, nanocellulose, cellulose nanocrystals, cellulose nanofibrils, bacterial nanocellulose, drug loading, controlled release, targeting, wound healing, toxicity, and biodistribution. Recent peer-reviewed studies were prioritized, while established older studies were retained for release-kinetic models. Because no preregistered protocol, duplicate screening process, or formal risk-of-bias assessment were used, the work should not be interpreted as a systematic review or meta-analysis.

Eligible sources included peer-reviewed research and focused reviews directly addressing preparation, functionalization, drug loading, release, biological performance, safety, or translation of lignin- or cellulose-derived carriers. Patents, commercial webpages, calculators, non-peer-reviewed summaries, and papers unrelated to lignocellulosic nanomedicine were excluded. Evidence was organized by material class, preparation route, loading mechanism, release mechanism, biomedical application, and translational limitation. Table 1 summarizes this search framework by linking each search theme to its keywords, sources, eligibility criteria, and extracted variables. The structure shows that the evidence synthesis was organized not only by material class but also by biomedical performance and translational safety.

Table 1. Literature search strategy and inclusion criteria

Search Theme	Keywords	Database/Source	Inclusion Criteria	Exclusion Criteria	Main Information Extracted
Nano-lignin systems	"nano-lignin drug delivery", "lignin nanoparticles controlled release", "stimuli-responsive lignin nanoparticles"	PubMed, Scopus, ScienceDirect, ACS	Nanoscale lignin particles, specific drug loading data, *in vitro* or *in vivo* efficacy evaluations	Macroscopic lignin composites, bulk wastewater treatments, non-medical applications	Synthesis methods, particle size, drug encapsulation efficiency, release kinetics.
Nanocellulose carriers	"nanocellulose drug delivery", "cellulose nanocrystals drug carrier", "bacterial cellulose wound dressing"	Web of Science, PubMed, Wiley, SpringerLink	CNC, CNF, or BNC as active carriers; clear release modeling	Microcrystalline cellulose (unless nanostructured), non-biomedical uses	Preparation techniques, functionalization strategies, bioadhesion, tissue compatibility.
Hybrid and composite platforms	"lignocellulosic nanomaterials nanomedicine", "cellulose-based hydrogel drug release", "lignin-coated nanocellulose"	Scopus, ScienceDirect, ACS	Synergistic use of lignin and cellulose within a single platform	Purely synthetic composites lacking biological origin	Mechanical enhancements, dual-drug loading capacity, synergistic biological effects.
Safety and	"lignin nanoparticle	PubMed, Web of	Studies providing	Purely hypothetical	Cytotoxicity limits,

translation	toxicity", "nanocellulose in vivo clearance", "biodistribution"	Science	cellular viability metrics, animal model biodistribution, or hematology	safety reviews without empirical experimental data	organ accumulation profiles, biodegradation pathways.

Results

Biologically derived drug delivery systems are defined as nanoscale platforms constructed from naturally occurring macromolecules. The main categories of these systems encompass polysaccharides (such as chitosan, alginate, hyaluronic acid, and cellulose), proteins (including albumin, gelatin, and silk fibroin), lipids (forming liposomes and solid lipid nanoparticles), lignocellulosic polymers (lignin and hemicelluloses), extracellular vesicles, and bacterial-derived materials. (Wijaya et al., 2021)

Biological-origin carriers may offer better compatibility and degradation than some synthetic or inorganic alternatives. Mammalian or microbial enzymes can metabolize several natural polymers, which may reduce tissue accumulation and chronic inflammation. Some biological carriers also have useful intrinsic activity. Chitosan is mucoadhesive and antimicrobial, for example, while lignin can scavenge radicals and act as an antioxidant. (Chai et al., 2021)

Natural nanomaterials also present practical problems. The most persistent of these is variation between batches. Molecular weight, polydispersity, and monomer composition can change with the biological source, growing region, and extraction method. Purification adds another constraint because endotoxins and residual extraction chemicals must be removed before sterilization and safety testing.

Lignin and cellulose are of particular interest because they are widely available in agricultural and industrial residues. Their functional groups and range of structures provide a relatively inexpensive starting point for biopolymer nanocarriers. (Wijaya et al., 2021)

Interest in biological-origin carriers is driven partly by the need for materials with acceptable compatibility and useful biological functions. Synthetic polymers are usually more uniform, whereas lignocellulosic materials are renewable and chemically diverse. Connecting waste valorization with biomedical use requires a clear account of how extraction and functionalization affect pharmacological performance. (Wijaya et al., 2021) The overall biomass-to-nanomedicine pathway is summarized in Figure 1.

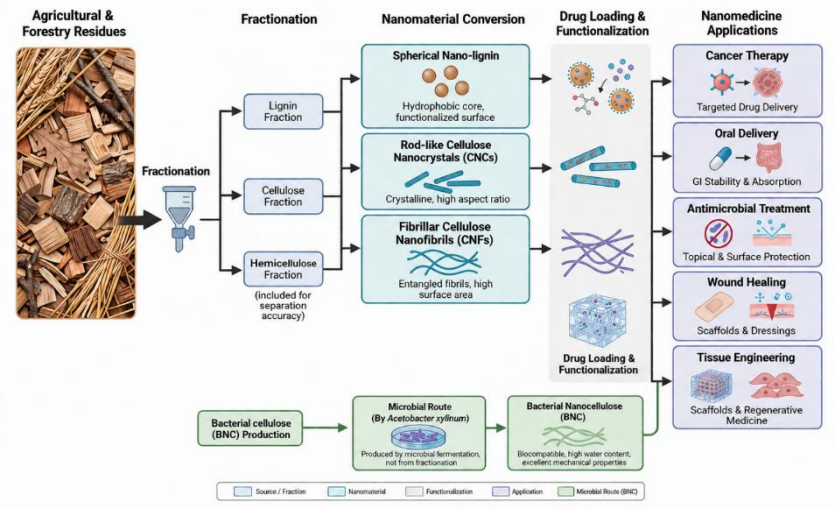

Figure 1. Biomass-to-nanomedicine overview. Agricultural and forestry residues are separated into lignin, cellulose, and hemicelluloses, followed by conversion into nano-lignin, cellulose nanocrystals (CNCs), cellulose nanofibrils (CNFs), and bacterial nanocellulose (BNC). The resulting carriers support drug loading and applications in cancer therapy, oral delivery, antimicrobial treatment, wound healing, and tissue engineering.

Lignin and Nano-Lignin as Drug Delivery Platforms

Structure and Sources of Lignin

Lignin is a complex, highly branched, amorphous aromatic biopolymer. It is synthesized in plants via the oxidative coupling of three primary monolignols: p-coumaryl, coniferyl, and sinapyl alcohols, which form p-hydroxyphenyl (H), guaiacyl (G), and syringyl (S) units, respectively. These units are interconnected through various ether (such as the dominant β-O-4 linkage) and carbon-carbon linkages, forming a rigid, recalcitrant three-dimensional network (Figure 2). (Wijaya et al., 2021)

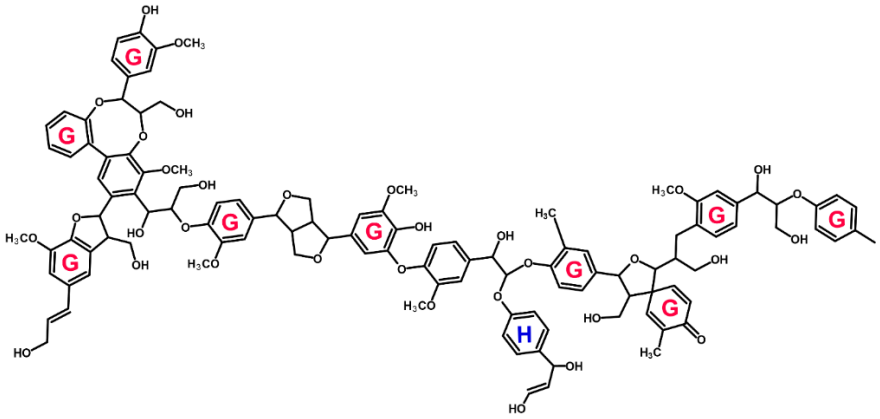

Figure 2. Proposed chemical structure of general softwood lignin oligomer.

The industrial extraction of lignin yields several technical variants, including kraft lignin, lignosulfonates, organosolv lignin, soda lignin, and enzymatic hydrolysis lignin. Each variant possesses a distinct physicochemical profile influenced heavily by the extraction severity. For instance, kraft lignin is highly condensed with high hydrophobicity, while lignosulfonates contain hydrophilic sulfonate groups, rendering them readily water-soluble. The fundamental relevance of lignin in nanomedicine stems from its high density of functional groups, specifically phenolic hydroxyls, aliphatic hydroxyls, methoxy, and carboxyl groups. These moieties confer antioxidant activity, broad-spectrum ultraviolet absorption, and extensive surface reactivity. Its intrinsic aromaticity and hydrophobicity make it potentially useful for capturing poorly water-soluble therapeutics. (Wijaya et al., 2021)

Preparation of Nano-Lignin

Transforming bulk, highly heterogeneous technical lignin into uniform nanoparticles (nano-lignin) requires precise top-down or bottom-up techniques to control particle dimensions and polydispersity. (Wijaya et al., 2021; Sipponen et al., 2018; Zhou et al., 2019a; Anonymous, 2025; Anonymous, 2023)

Solvent exchange, also nanoprecipitation, is the most common bottom-up method. Lignin is dissolved in an organic solvent, such as tetrahydrofuran, ethanol, or acetone, and then mixed rapidly with an antisolvent, usually water. Solvent diffusion into the aqueous phase causes supersaturation, and hydrophobic interactions drive the formation of spherical particles. The method provides good control over particle size but uses substantial volumes of solvent that must later be recovered. Dialysis relies on the same general principle, although solvent exchange across a semipermeable membrane is slower. (Sipponen et al., 2018; Anonymous, 2025)

known as Acid precipitation involves dissolving lignin in an alkaline solution and rapidly dropping the pH using an acid, such as hydrochloric or sulfuric acid. The protonation of phenolic hydroxyl groups reduces lignin's aqueous solubility, forcing the rapid precipitation of nanoparticles. While highly scalable and cost-effective, this method frequently results in a broader polydispersity index and may degrade pH-sensitive active pharmaceutical ingredients. (Wijaya et al., 2021) The transient strongly acidic window is mechanistically important: acid-labile payloads such as ester- or acetal-containing prodrugs can undergo hydrolytic cleavage, while peptide and protein drugs may denature and aggregate, so post-loading after particle formation or buffered/partial-neutralization protocols are preferable for such agents.

Ultrasonication is a top-down method in which acoustic cavitation produces the shear needed to break lignin aggregates into particles, 10 to 50 nm in diameter. It avoids chemical precipitants, although hydroxyl radicals formed during treatment may alter the lignin. Mechanistically, cavitation-generated hydroxyl radicals attack the macromolecule by cleaving β-O-4 aryl-ether bonds and hydroxylating aromatic rings, driving both depolymerization and radical repolymerization; because phenolic content governs radical scavenging, this shifts the molecular-

weight distribution and can measurably change the antioxidant capacity that often motivates using lignin, so sonication conditions should be controlled and the antioxidant activity of the product verified rather than assumed. Other methods include miniemulsion polymerization, microfluidic mixing, and spray drying. Miniemulsion methods crosslink lignin at the interface of oil-in-water droplets to make core-shell capsules. Microfluidic devices provide continuous and reproducible mixing, whereas spray drying converts lignin solutions into stable micro- or nanoscale powders by rapid solvent evaporation. (Chai et al., 2021; Anonymous, 2023) Figure 3 shows the preparation routes of nanolignin and Table 2 compares the operating principles, particle features, advantages, limitations, and drug-delivery uses of these methods. Solvent exchange gives relatively close control over hydrophobic-drug encapsulation. Acid precipitation and spray drying are easier to scale, but size control or processing stress may become limiting.typically

Table 2. Preparation methods for nano-lignin drug delivery systems

Method	Principle	Typical Particle Characteristics	Advantages	Limitations	Suitability for Drug Delivery
Solvent exchange / Nanoprecipitation	Solvent displacement leading to rapid supersaturation and self-assembly.	50-300 nm, spherical morphology, low PDI.	High reproducibility, narrow size distribution, facile drug encapsulation.	High solvent usage, requires intensive solvent recovery protocols.	Excellent for hydrophobic drugs co-precipitated directly with lignin.
Ultrasonication	Acoustic cavitation generates mechanical shear and localized heat.	10-100 nm, irregular to spherical shapes.	Surfactant-free, environmentally greener process.	High energy demand, potential oxidative degradation of sensitive drugs.	Favorable for post-loading or creating pure nano-lignin as active antioxidants.
Acid precipitation	pH drop protonates hydroxyls, decreasing solubility to force precipitation.	100-500 nm, broader PDI.	Simple, very low cost, highly scalable.	Wide size distribution, acidic conditions may degrade biologicals.	Moderate; requires strict pH control when formulated with sensitive therapeutic agents.
Miniemulsion	Lignin crosslinked at the interface of stabilized oil-in-water droplets.	50-300 nm, hollow or core-shell capsules.	Allows encapsulation of massive drug payloads in a liquid core.	Requires surfactants and chemical crosslinkers.	Ideal for targeted, highly stimuli-responsive release systems.
Spray drying	Atomization of lignin solution followed by rapid thermal solvent evaporation.	1-5 µm (can be tuned to sub-micron).	Highly scalable, continuous process, solid powder recovery.	Larger particle sizes, thermal stress on active pharmaceutical ingredients.	Best utilized for oral delivery formulations or inhalable powders.

Drug-Loading Mechanisms in Nano-Lignin

Lignin can load drugs through several interactions. π-π stacking between its aromatic rings and aromatic drug molecules is especially relevant to hydrophobic anticancer agents such as doxorubicin and paclitaxel. Its phenolic and aliphatic hydroxyl groups can also form hydrogen bonds with drug molecules. (Chai et al., 2021; Figueiredo et al., 2017; Figueiredo et al., 2018; Zhou et al., 2019b)

Lignin carriers are often studied for poorly water-soluble drugs because self-assembly in water produces a hydrophobic core. Entrapment in this core can give high encapsulation efficiencies, although the reported values depend on the formulation. Curcumin is one frequently studied example. Surface adsorption and electrostatic interactions become more important when chemical modification gives lignin a defined charge. Pure lignin particles generally retain hydrophilic drugs less effectively, so core-shell structures or covalent attachment may be needed to limit premature release. (Wijaya et al., 2021; Zhou et al., 2019a)

Controlled and Stimuli-Responsive Release from Nano-Lignin

Drug release from nano-lignin depends on diffusion through the matrix and on gradual particle erosion or degradation. Researchers have also introduced pH-, redox-, or enzyme-sensitive elements to alter release under selected physiological conditions. (Zhou et al., 2019a; Anonymous, 2022a; Anonymous, 2024)

The ionization of lignin's phenolic hydroxyl and carboxyl groups changes with pH. Particles containing acid-cleavable hydrazone bonds or metal-coordination complexes can therefore release drugs faster at pH 5.5 to 6.5 than at physiological pH 7.4. Disulfide crosslinks provide a redox-sensitive route because intracellular glutathione can break these bonds. Enzyme-sensitive lignin carriers have mainly been studied for agricultural delivery; their value in localized human therapy remains theoretical. Release is often non-Fickian because diffusion occurs alongside polymer relaxation or degradation. The Korsmeyer-Peppas equation ($Q_t/Q\infty = K\_KP\ t^n$) uses the exponent n to distinguish these mechanisms. The Hixson-Crowell relation ($Q_0^{1/3} - Q_t^{1/3} = K\_HC\ t$) is applicable when a changing particle surface area controls dissolution. (Anonymous, 2024; Machado et al., 2020; Korsmeyer et al., 1983; Hixson & Crowell, 1931)

Biomedical Applications of Nano-Lignin

Nano-lignin has been tested in several biomedical settings. In cancer models, the enhanced permeability and retention effect may contribute to tumor accumulation, but this effect varies among human tumors and is less predictable than in many preclinical models. Targeting ligands such as folic acid can increase cellular uptake. In one line of work, folic acid-conjugated nano-lignin carrying hydroxycamptothecin produced greater tumor suppression and less systemic toxicity than the free drug. (Figueiredo et al., 2017; Figueiredo et al., 2018; Zhou et al., 2019b)

Lignin has shown antibacterial activity in experimental systems, including effects associated with membrane damage and oxidative stress. Combining nano-lignin with silver nanoparticles or antibiotics may strengthen antimicrobial action, while its antioxidant activity may also support wound repair by reducing reactive oxygen species. For oral delivery, lignin particles can protect acid-sensitive or poorly soluble compounds in the stomach. Curcumin-loaded formulations, for example, have remained stable in simulated gastric fluid and then released the drug under intestinal conditions in preclinical studies. Other reported uses include transdermal delivery, antioxidant treatment, and theranostic imaging, where the carrier also contributes to image contrast. (Alqahtani et al., 2019; Anonymous, 2022b; Anonymous, 2023b) damage

Advantages and Limitations of Nano-Lignin

Nano-lignin is renewable, inexpensive at the raw-material stage, and well suited to hydrophobic compounds because of its aromatic structure. This affinity may help formulate drugs with poor water solubility. Lignin's antioxidant activity can also protect sensitive compounds, including vitamins and photosensitizers, from oxidation or ultraviolet exposure. (Wijaya et al., 2021; Zhou et al., 2019a)

The main limitation is structural heterogeneity. Lignin composition changes during biosynthesis and industrial pulping, so molecular weight, solubility, and functional-group density vary with source and process. These differences affect particle size and drug-release behavior from one batch to another. Technical lignins may also contain sulfur or trace metals, which complicate toxicology and regulatory assessment. (Wijaya et al., 2021; Anonymous, 2025)

Nano-lignin is not always an inert carrier because its antioxidant properties can contribute to the biological response. Clinical development is nevertheless restricted by the variability of the macromolecule. Fractionation and purification will be needed to define reproducible lignin feedstocks before nanoprecipitation and to meet pharmaceutical quality requirements. (Anonymous, 2025)

Cellulose-Based Nanocarriers for Drug Delivery

Structure and Sources of Cellulose

Cellulose is an unbranched linear homopolymer of β-1,4-linked D-glucopyranose units. Hydrogen bonding between parallel chains produces ordered crystalline regions separated by more flexible amorphous domains. Cellulose is extracted from wood pulp, cotton, agricultural residues, tunicates, and algae, and some bacterial strains synthesize it extracellularly. Primary and secondary hydroxyl groups along the chain provide sites for chemical modification, which makes cellulose a useful structural material for drug-delivery systems. (Plackett et al., 2014; Bacakova et al., 2019)

Types of Nanocellulose

Nanocellulose is classified by its morphology and source, both of which influence its physical properties and pharmaceutical use. (Plackett et al., 2014; Bacakova et al., 2019)

Cellulose Nanocrystals (CNCs): CNCs are produced by acid hydrolysis, which removes much of the amorphous cellulose and leaves rigid, highly crystalline rods. Typical dimensions are 5 to 20 nm in width and 100 to 500 nm in length. Their mechanical strength, surface area, and, after sulfuric-acid hydrolysis, negative charge support electrostatic drug loading and surface modification. (Plackett et al., 2014; Seo et al., 2020; Kim et al., 2020; Dong et al., 2012; Barbosa et al., 2016)

Cellulose Nanofibrils (CNFs): CNFs are produced by mechanical shear, often after enzymatic or chemical pretreatment, and retain both crystalline and amorphous regions. They typically consist of long, flexible fibrils with diameters of approximately 5–100 nm and lengths ranging from several to tens of micrometers, resulting in a high aspect ratio. Their entangled fibrillar structure forms viscous hydrogels at low concentrations, making them useful as matrices for sustained local or topical drug release. (Masruchin et al., 2017; Liu et al., 2020; Auvinen et al., 2022; Li et al., 2021; Bi et al., 2023; Auvinen et al., 2020; Chen et al., 2021; Zhao et al., 2015)

Bacterial Nanocellulose (BNC): BNC is synthesized extracellularly by Komagataeibacter species and consists of an ultrafine three-dimensional fibrillar network composed of nanofibers typically 20–100 nm in diameter. Unlike plant-derived cellulose, BNC is produced without lignin or hemicelluloses and retains large amounts of water while exhibiting excellent flexibility and generally favorable biocompatibility in the tested models. These properties support its use in wound dressings, topical drug delivery, and tissue engineering scaffolds. (Gupta et al., 2020; Rojewska et al., 2020; Tong et al., 2017; Madanhire et al., 2026; Ebadati et al., 2022; Berglund et al., 2023; Moritz et al., 2014; Mo et al., 2025; Won et al., 2025; Munawaroh et al., 2023; Anonymous, 2017; Lasopha & Lasopha, 2024)

Table 3. Comparison of cellulose nanomaterials for drug delivery

Nanocellulose Type	Source	Morphology	Key Properties	Drug Delivery Advantages	Limitations	Main Biomedical Applications
Cellulose Nanocrystals (CNCs)	Wood pulp, cotton, agricultural waste	Rigid, rod-like crystals (100-500 nm length)	High crystallinity, negative surface charge (when sulfated)	Large surface area for molecular binding; high colloidal stability	Limited inherent capability to form standalone stable hydrogels	Targeted systemic nanocarriers, composite reinforcers
Cellulose Nanofibrils (CNFs)	Wood pulp, agricultural waste	Flexible, entangled fibrils (nanoscale width, micrometric length)	Both crystalline and amorphous domains; rapidly forms viscous gels	Excellent rheological modifier, provides sustained diffusion-based release	High energy cost of production, extreme difficulty in redispersion upon drying	Injectable hydrogels, oral extended-release matrices
Bacterial Nanocellulose (BNC)	Bacterial fermentation (*K. xylinus*)	3D interconnected pure nanofibril network	Ultra-high purity, massive water retention capacity	Excludes immune-triggering plant impurities; matrix structurally mimics the extracellular matrix	Slower, significantly more expensive bottom-up production	Advanced wound dressings, transdermal patches, tissue scaffolds

Preparation Methods of Nanocellulose

Preparation conditions affect both cytocompatibility and release behavior. Sulfuric-acid hydrolysis introduces sulfate half-esters on CNC surfaces. These groups stabilize aqueous suspensions but may produce biological interactions that differ from those of uncharged cellulose. High-pressure homogenization, super grinding microfluidization and ultrasonication can produce CNFs without adding new surface groups, although all processes consume considerable energy. TEMPO-mediated oxidation before fibrillation converts primary hydroxyls to carboxylates, improving dispersion and providing sites for drug conjugation. Residual catalyst and acid must be removed because they can be cytotoxic. (Seo et al., 2020; Kim et al., 2020; Plappert et al., 2019; Akhlaghi et al., 2013; Wang & Roman, 2011; Xu et al., 2019; Anonymous, 2022c) Figure 2 summarizes the main preparation and functionalization routes.

Functionalization of Cellulose-Based Nanocarriers

Unmodified nanocellulose loads drugs mainly through hydrogen bonding, van der Waals forces, and other weak interactions. Chemical functionalization is used when higher loading or systemic targeting is required. TEMPO oxidation introduces carboxyl groups that bind cationic drugs or support EDC/NHS coupling to amine-containing ligands. Amination adds positive charge and can improve binding to anionic drugs, siRNA, or DNA. Polymer grafting provides further control. PEGylation can reduce protein adsorption and phagocytic clearance, while temperature-responsive polymers such as poly(N-isopropylacrylamide) can support release on demand. (Masruchin et al., 2017; Liu et al., 2020; Anonymous, 2019; Anonymous, 2023c)

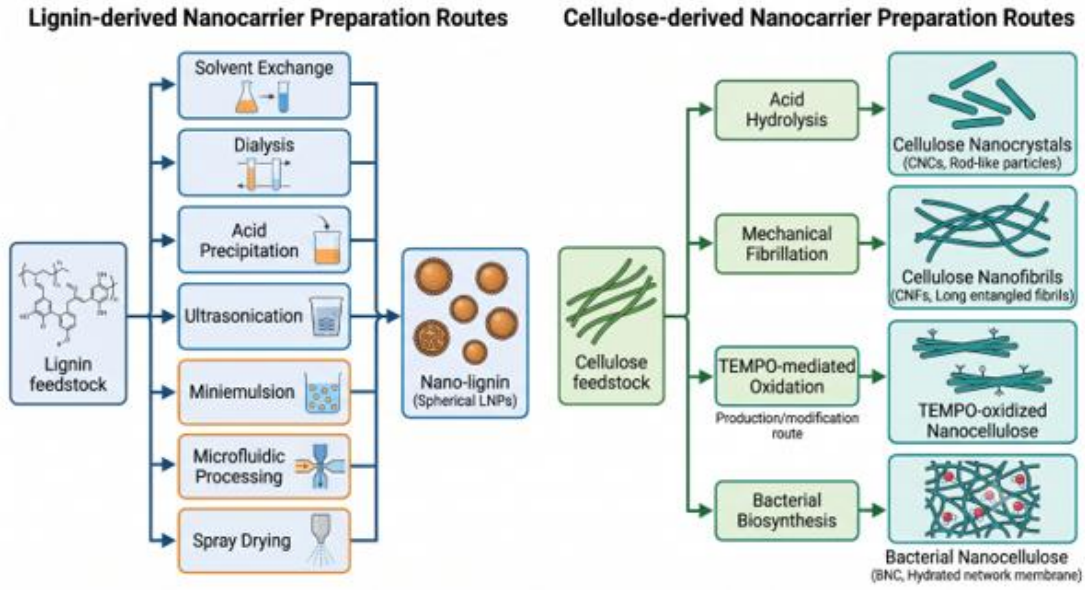

Figure 3. Principal preparation routes for lignin- and cellulose-derived nanocarriers. Nano-lignin routes include solvent exchange, dialysis, acid precipitation, ultrasonication, miniemulsion, microfluidic processing, and spray drying. Nanocellulose routes include acid hydrolysis to produce CNCs, mechanical fibrillation to produce CNFs, TEMPO-mediated oxidation, and bacterial biosynthesis of BNC.

Drug-Loading Mechanisms in Cellulose-Based Systems

Cellulose systems load drugs either by trapping them within a three-dimensional network or by adsorption to the surface. Entrapment is common in CNF and BNC hydrogels, whereas electrostatic adsorption is important when cationic drugs bind to sulfated CNCs. A drug can also be attached covalently through a linker that responds to a local stimulus. This approach can reduce early burst release and delay release until the carrier reaches a tumor or infected wound. (Chai et al., 2021; Figueiredo et al., 2017; Figueiredo et al., 2018; Zhou et al., 2019b; Seo et al., 2020; Kim et al., 2020; Akhlaghi et al., 2013; Ndong Ntoutoume et al., 2016; Yusefi et al., 2022) Figure 4 compares the main loading interactions in lignin and functionalized cellulose carriers.on

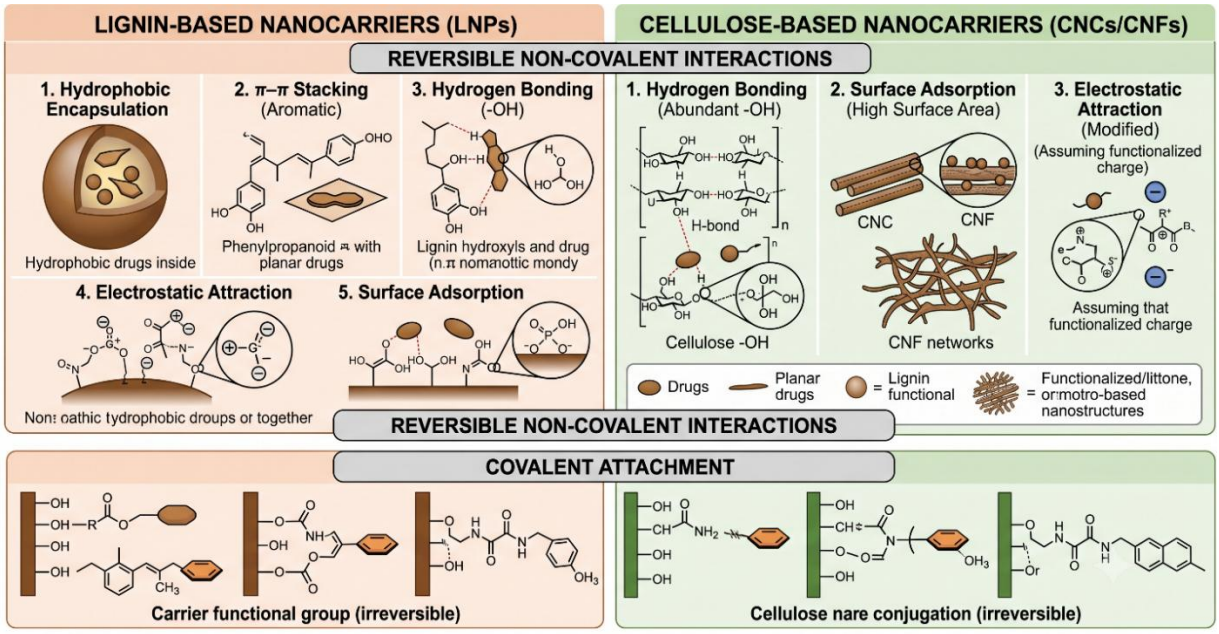

Figure 4. Drug-loading interactions in lignin- and cellulose-based nanocarriers. The schematic compares hydrophobic encapsulation, π-π stacking, hydrogen bonding, electrostatic attraction, surface adsorption, and optional covalent conjugation, while distinguishing reversible non-covalent interactions from covalent attachment.

Release Behavior of Cellulose-Based Carriers

Release from nanocellulose networks is usually diffusion controlled. In CNF and BNC hydrogels, entangled fibrils create tortuous paths that slow drug movement and can sustain release from hours to weeks. Swelling may contribute, but rapid erosion is unlikely because humans do not produce cellulases. Release therefore depends mainly on pore size, crosslink density, and the strength of drug-polymer interactions. (Masruchin et al., 2017; Liu et al., 2020; Auvinen et al., 2022; Li et al., 2021; Bi et al., 2023; Auvinen et al., 2020; Chen et al., 2021; Zhao et al., 2015; Xu et al., 2019; Jeong et al., 2022) Figure 5 summarizes the physiological triggers and corresponding release responses.

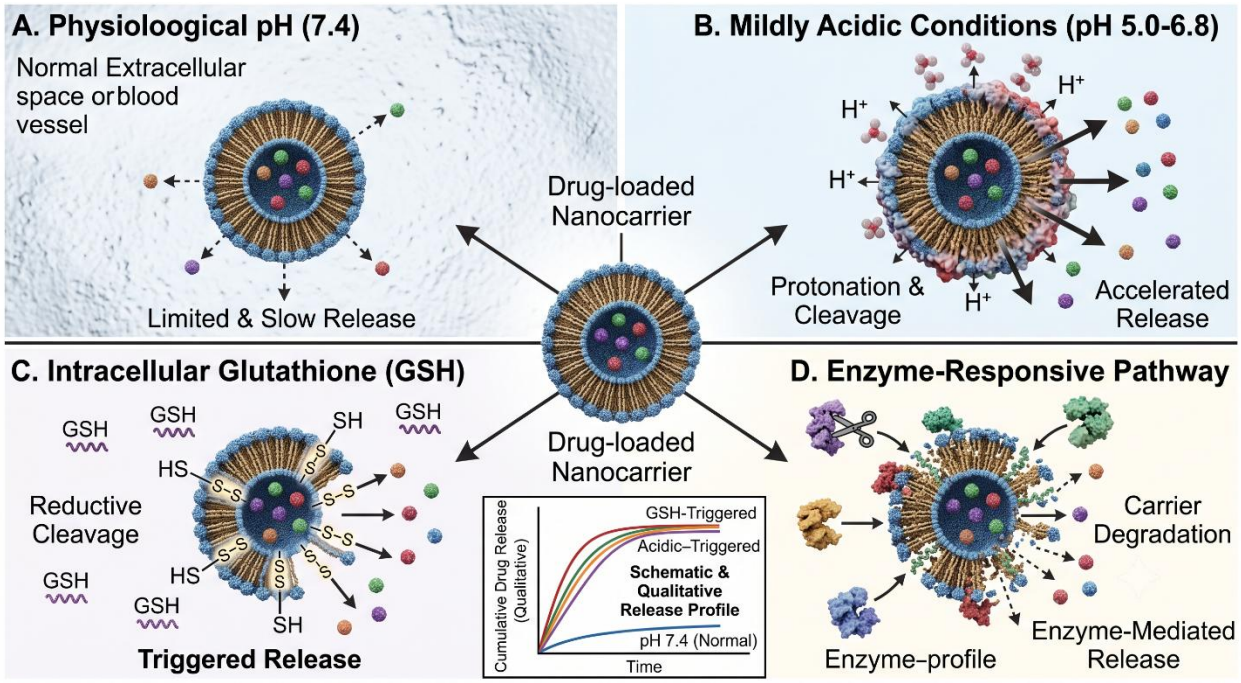

Figure 5. Stimuli-responsive drug-release mechanisms. The four pathways comprise limited release at physiological pH 7.4, accelerated release under mildly acidic conditions through protonation or acid-cleavable linkers, intracellular glutathione-mediated reduction of disulfide bonds, and enzyme-responsive carrier degradation. The release-profile inset is qualitative and schematic.

Biomedical Applications of Cellulose-Based Drug Delivery

Cellulose-based systems have been studied most extensively for localized delivery. BNC dressings are used or investigated for burns and chronic ulcers, where they retain moisture and can carry silver nanoparticles or antibiotics. Cellulose derivatives can also protect oral drugs from gastric acid. Carboxymethyl cellulose and CNC composite hydrogels may remain contracted in the stomach and swell at intestinal pH. For cancer delivery, ligands attached to CNC surfaces can promote uptake of agents such as paclitaxel and ellipticine by selected tumor cells, although most evidence remains preclinical. (Seo et al., 2020; Kim et al., 2020; Ndong Ntoutoume et al., 2016; Yusefi et al., 2022; Kumar & Chauhan, 2022)

Nano-lignin is useful mainly as an active hydrophobic particle, whereas nanocellulose is valued for its mechanical properties and affinity for water. CNCs provide a surface for controlled chemical modification. Their systemic use, however, raises questions because human tissues cannot enzymatically degrade cellulose. Current evidence therefore favors topical, oral, or localized implantable uses over repeated systemic administration. (Dong et al., 2012; Anonymous, 2019; Anonymous, 2023c) Figure 6 summarizes the structural and functional differences among CNCs, CNFs, and BNC.

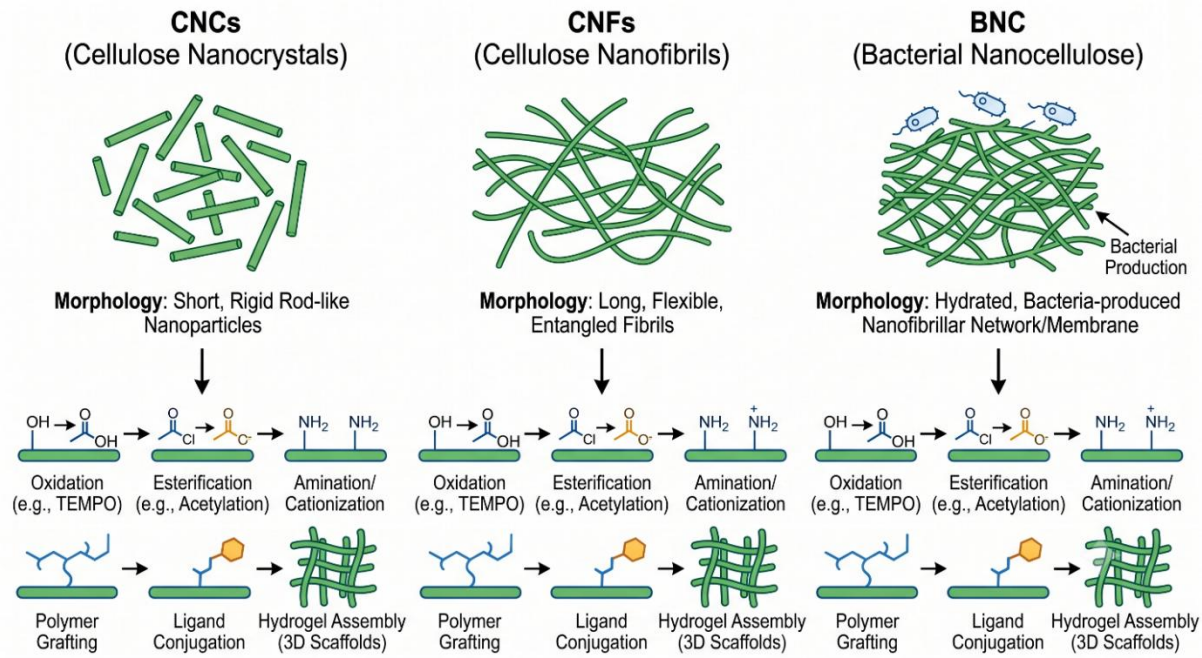

Figure 6. Comparison of the principal nanocellulose classes. CNCs are depicted as rigid rod-like particles, CNFs as flexible entangled fibrils, and BNC as a hydrated bacteria-produced nanofibrillar network. Representative modification routes include oxidation, esterification, amination, polymer grafting, ligand conjugation, and hydrogel assembly.

Comparative Analysis: Nano-Lignin vs Cellulose-Based Nanocarriers

The main difference between nano-lignin and nanocellulose is their chemistry. Lignin is aromatic and relatively hydrophobic, with intrinsic antioxidant activity. Cellulose is aldohexose in nature, hydrophilic, and comparatively inert. Nano-lignin therefore tends to retain poorly soluble aromatic drugs, whereas nanocellulose networks are better suited to aqueous formulations and local depots. (Wijaya et al., 2021; Plackett et al., 2014; Zheng et al., 2019) Table 4 compares structure, polarity, drug affinity, degradation, safety, scalability, and regulatory readiness. Carrier selection depends on the intended use: nano-lignin favors hydrophobic payloads, while CNCs and CNF/BNC systems provide surfaces or networks for aqueous and localized delivery.

Table 4. Comparative evaluation of nano-lignin and cellulose-based nanocarriers

Parameter	Nano-Lignin	Cellulose Nanocrystals (CNCs)	Cellulose Nanofibrils (CNFs) / BNC	Critical Interpretation
Chemical Structure	Amorphous, highly branched polyphenolic network.	Rigid, highly crystalline linear polysaccharide.	Linear polysaccharide; semicrystalline/amorphous networks.	Lignin's aromaticity dictates hydrophobic drug affinity; cellulose suits physical hydrogel entrapment.

Hydrophobicity / Hydrophilicity	Highly hydrophobic core, amphiphilic exterior.	Hydrophilic surface, dispersible in water.	Extremely hydrophilic, massive water retention.	Formulators must strictly match drug polarity with the nanocarrier's intrinsic chemistry.
Drug Affinity	High for hydrophobic and aromatic drugs (π-π stacking).	High for ionic and hydrophilic molecules.	High for hydrophilic molecules via water entrapment.	Nano-lignin solves solubility issues; cellulose prolongs aqueous drug residency.
Biodegradability	Slowly degradable *in vivo* (via oxidative pathways and macrophages).	Not enzymatically degradable by humans; relies on macrophage clearance.	Non-degradable *in vivo*; topically removable or excreted via GI tract.	Lack of human cellulases limits systemic intravenous use of cellulose compared to other bio-polymers.
Toxicity	Very low, though sensitive to source chemical impurities.	Very low, highly biocompatible.	Very low; BNC is practically inert and immune-evasive.	BNC represents the safest option for direct tissue contact; lignin requires stringent purification.
Scalability & Cost	Low material cost, but standardization is difficult.	High material cost for pure CNCs, established industrial scaling.	BNC is slow/costly to ferment; CNF scaling is energy-intensive.	Cellulose processing is far more established at the industrial level than lignin nano-formulation.
Regulatory Readiness	Low; heavily hampered by structural heterogeneity.	Moderate; standardized extraction methods exist.	High (BNC); already used in FDA-approved commercial wound dressings.	Cellulose is closer to widespread systemic clinical translation than lignin.

Hybrid Lignin-Cellulose Drug Delivery Systems

Lignin and cellulose have complementary properties, which has led to growing interest in hybrid systems. Lignin contributes antioxidant or antimicrobial activity but provides little mechanical support in a hydrogel. Cellulose forms strong scaffolds but has limited intrinsic biological activity. (Wijaya et al., 2021; Plackett et al., 2014)

Hybrid materials include cellulose-reinforced lignin particles and lignin-cellulose hydrogels. In one example, adding mesoporous polydopamine and lignin to a CNF hydrogel reduced the initial antibiotic burst and increased tensile strength fivefold relative to the unmodified CNF gel. The simultaneous mechanical reinforcement and burst suppression is difficult to explain as a simple physical mixture and is more consistent with true interfacial synergy: the flexible cellulose network carries mechanical load and arrests crack propagation (mitigating lignin brittleness), while

embedding lignin particles within the matrix imposes a tortuous diffusion barrier that converts a burst profile toward sustained release. Genuine synergy should nonetheless be confirmed with additive-control experiments, since many reported hybrids remain structural composites rather than synergistic systems. Lignin coatings can also add ultraviolet shielding and antimicrobial activity to nanocellulose matrices used in wound dressings or tissue scaffolds. (Anonymous, 2022b; Anonymous, 2017; Patel et al., 2021; Shi et al., 2022; Wu et al., 2026)

demonstrably Hybrid systems can address some limitations of each component. Cellulose may reduce the brittleness and burst release associated with lignin-rich formulations, while lignin adds biological activity to cellulose networks. The resulting material may support more than one drug and combine structural and therapeutic functions. (Wijaya et al., 2021; Plackett et al., 2014; Anonymous, 2022b; Patel et al., 2021)

Drug Delivery Routes and Application-Specific Design

Carrier design depends on the physiological barriers associated with the chosen route of administration.

Oral Drug Delivery

Oral carriers must tolerate changes in pH and exposure to digestive enzymes. Crosslinked nanocellulose beads can resist gastric conditions and then swell at intestinal pH, making them useful for colon-targeted delivery. Lignin is also relatively resistant to acid and can protect hydrophobic payloads in the stomach before intestinal release. (Alqahtani et al., 2019; Li et al., 2021; Auvinen et al., 2020; Xu et al., 2019; Jeong et al., 2022)

Transdermal and Topical Delivery

The skin is suitable for local sustained delivery. BNC patches retain moisture, allow gas exchange, and release antimicrobial or anti-inflammatory drugs into the wound area. Adding nano-lignin may provide antioxidant activity by scavenging reactive oxygen species, although the magnitude of any improvement in tissue repair depends on the formulation and model. (Gupta et al., 2020; Rojewska et al., 2020; Tong et al., 2017; Madanhire et al., 2026; Ebadati et al., 2022; Berglund et al., 2023; Moritz et al., 2014; Mo et al., 2025; Won et al., 2025; Anonymous, 2017; Lasopha & Lasopha, 2024; Shi et al., 2022; Wu et al., 2026)

Injectable Systems

Injectable carriers require sterility, hemocompatibility, and narrow control of particle size, commonly below 200 nm. Some CNF hydrogels undergo a sol-gel transition near body temperature and can form a local drug depot after injection. Intravenous CNC and nano-lignin formulations often use PEGylation to reduce rapid uptake by the reticuloendothelial system. Because blood contains no cellulase, injected CNCs must be cleared as small particles or taken up by macrophages. Their long-term fate remains an important safety question. (Dong et al., 2012; Anonymous, 2019; Anonymous, 2023c)

Cancer Therapy

Tumor delivery can rely on passive accumulation through the enhanced permeability and retention effect or on receptor-mediated uptake. Nano-lignin can carry poorly soluble drugs such as docetaxel, paclitaxel, and 5-fluorouracil, and pH-sensitive formulations may release them more rapidly in acidic tumor environments. Hybrid lignin-cellulose systems containing magnetic particles have also been studied for MRI tracking and heat-triggered release. (Figueiredo et al., 2017; Figueiredo et al., 2018; Zhou et al., 2019b; Anonymous, 2023b; Seo et al., 2020; Kim et al., 2020; Ndong Ntoutoume et al., 2016; Yusefi et al., 2022; Kumar & Chauhan, 2022)

Antimicrobial and Wound-Healing Applications

Antimicrobial delivery is an important part of wound care, particularly when resistant organisms are present. BNC matrices can release silver ions gradually, damaging bacterial membranes while limiting exposure of fibroblasts. Lignin may add antibacterial activity and could reduce the amount of conventional antibiotic needed, although this depends on the formulation. (Anonymous, 2022b; Gupta et al., 2020; Tong et al., 2017; Moritz et al., 2014; Mo et al., 2025; Won et al., 2025; Anonymous, 2017; Lasopha & Lasopha, 2024; Shi et al., 2022; Wu et al., 2026)

The route of administration strongly influences the choice between lignin and cellulose. Because cellulose is not enzymatically degraded in humans, topical and oral uses are easier to justify: the material can be removed or excreted. Nano-lignin may be more suitable for injection if its degradation and purity can be controlled. (Anonymous, 2022a; Alqahtani et al., 2019; Anonymous, 2019) Figure 7 relates administration route to carrier behavior, local release, and therapeutic outcome. Table 5 compares each application with the preferred carrier, mechanism, and level of supporting evidence. BNC has the most established role in local wound care, whereas cancer, oral, and injectable-depot applications rely more heavily on formulation-specific preclinical or pharmacokinetic studies.

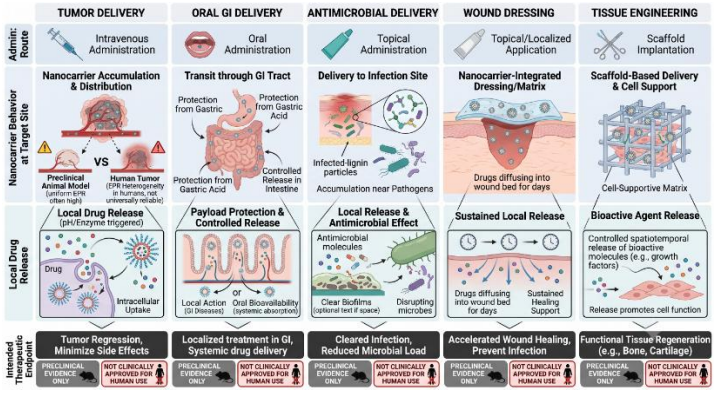

Figure 7. Application-specific biomedical pathways for lignocellulosic nanocarriers. The principal routes include tumor delivery, oral gastrointestinal delivery, antimicrobial delivery, wound dressing, and tissue-engineering scaffolds. Each pathway links administration, carrier behavior, local drug release, and the intended therapeutic endpoint; enhanced permeability and retention is identified as heterogeneous in human tumors, and preclinical evidence is distinguished from clinical use.

Table 5. Biomedical applications of nano-lignin and cellulose-based nanocarriers

Application Field	Preferred Material	Primary Therapeutic Function	Mechanistic Advantage	Supported By
Cancer Therapy	Nano-Lignin, CNCs	Delivery of hydrophobic chemotherapeutics (e.g., paclitaxel); active targeting only where ligand-mediated, otherwise passive (EPR) accumulation.	High encapsulation efficiency via π-π stacking; EPR effect accumulation.	*In vitro* viability assays; xenograft *in vivo* models.
Wound Healing	Bacterial Cellulose (BNC)	Sustained release of antimicrobials and moisture regulation.	Matrix mimics extracellular matrix; highly flexible and pure.	Clinical application; extensive *in vivo* wound models.
Oral Delivery	Lignin, CNF hydrogels	Protection of sensitive drugs through gastric environments.	Acid resistance prevents burst release; swelling occurs in intestinal pH.	Pharmacokinetic bioavailability studies.
Injectable Depots	CNF, Hybrid hydrogels	Sustained localized release of proteins or analgesics.	Sol-gel transition confines the therapeutic payload to the injection site.	*In vitro* rheological tests; subcutaneous *in vivo* tracking.

Safety, Biocompatibility, and Toxicity

A biological origin does not guarantee that a nanomaterial is safe. Reducing lignin or cellulose to the nanoscale increases surface area and reactivity, which may alter membrane interactions, oxidative stress, and immune responses. (Dong et al., 2012; Anonymous, 2019; Anonymous, 2023c)

Most in vitro studies report low cytotoxicity for nano-lignin and nanocellulose in cell lines such as fibroblasts and Caco-2 cells. In vivo behavior is less certain. After intravenous administration, CNCs can accumulate in the liver and spleen through macrophage uptake. Acute toxicity is often limited in the available studies, but mammals lack enzymes that digest cellulose, so the risk of long-term accumulation has not been resolved. (Dong et al., 2012; Anonymous, 2019; Anonymous, 2023c)

Nano-lignin follows a different metabolic path because of its aromatic structure. Biodistribution studies report liver accumulation, and its antioxidant activity has reduced acetaminophen-related liver injury in some experimental models. Technical lignin may also contain sulfur residues from kraft process, however, and these impurities must be removed before formulation because they can provoke inflammation. (Anonymous, 2022a)

Table 6 compares cytotoxicity, hemocompatibility, biodegradation, and immunogenicity. Short-term cytocompatibility is generally favorable, but clearance, protein-corona formation, and the effects of chronic or repeated exposure remain uncertain, especially after systemic administration.

Table 6. Safety considerations for nano-lignin and cellulose-based drug delivery systems

Safety Parameter	Relevance to Drug Delivery	Nano-Lignin Considerations	Cellulose-Based Considerations	Current Knowledge Gap
Cytotoxicity	Determines the maximum safe therapeutic dosage.	Very low; can actively protect cells from oxidative stress.	Very low; BNC has shown low toxicity in the mammalian-cell systems tested.	Long-term high-dose exposure effects over months.
Hemocompatibility	Crucial for direct intravenous injection protocols.	Moderate; depends heavily on final surface charge and purity.	High, provided surface sulfate groups do not trigger complement activation.	Precise protein corona formation mechanisms *in vivo*.
Biodegradation	Prevents chronic systemic bioaccumulation.	Degradable via oxidative species and macrophage digestion.	Non-degradable *in vivo*; relies purely on physical clearance.	Precise systemic half-lives and clearance routes.
Immunogenicity	Avoidance of anaphylaxis or rejection.	Potential risks stem entirely from industrial chemical impurities.	Low, but rigid CNC needles may mimic pathogenic fibers if dimensions are unchecked.	Immune responses to chronic, repeated administration.

The limited long-term pharmacokinetic and toxicology data are a major barrier to clinical use. Regulators are unlikely to accept parenteral applications until degradation rates and clearance pathways have been characterized in suitable animal models. (Anonymous, 2022a; Dong et al., 2012; Anonymous, 2019; Anonymous, 2023c) Quantitative pharmacokinetic and biodistribution data remain sparse for these carriers: for intravenous cellulose the dominant fate is reticuloendothelial capture in liver and spleen with no cellulase-mediated degradation, while nano-lignin follows a distinct oxidative hepatic route; elimination half-lives and mass-balance excretion pathways are largely not yet established and constitute a key translational gap.

Drug Release Kinetics and Mechanistic Modeling

Mathematical models help relate release profiles to possible mechanisms. Biopolymer matrices rarely follow ideal zero-order behavior, so the selected model must reflect the structure of the carrier and the range of data being fitted.

Release profiles from highly porous nanocellulose hydrogels frequently approximate first-order kinetics, where the release rate depends heavily on the concentration of the drug remaining within the matrix. The Higuchi model, based on Fickian diffusion from an insoluble matrix, is widely applicable to CNF and BNC hydrogels where the structural matrix remains fully intact while the drug diffuses outward through solvent-filled pores. (Auvinen et al., 2022; Auvinen et al., 2020; Higuchi, 1963)

The Korsmeyer-Peppas model uses the exponent n to classify release behavior. Values of n at or below 0.45 indicate predominantly Fickian diffusion, whereas values between 0.45 and 0.89 suggest a combination of diffusion and polymer swelling or relaxation. Nano-lignin often falls in the latter range because diffusion and slow matrix degradation occur together. The Hixson-Crowell equation ($Q_0^{1/3} - Q_t^{1/3} = K\_HC\ t$) instead describes systems in which erosion changes particle surface area during release. (Anonymous, 2022a; Anonymous, 2024; Korsmeyer et al., 1983; Hixson & Crowell, 1931) Table 7 lists the assumptions and limitations of the main models. Higuchi is suited to stable diffusion-controlled hydrogels, Korsmeyer-Peppas to early mixed transport, and Hixson-Crowell to eroding particles.

Table 7. Common mathematical models used for drug release analysis

Model	Equation	Main Assumption	Suitable System	Limitation
Zero-order	$Q_t = Q_0 + K_0 t$	Overall release rate remains constant.	Ideal targeted osmotic pumps.	Rarely fits simple swelling hydrogels perfectly.
First-order	$\ln Q_t = \ln Q_0 - K_1 t$	Release is directly proportional to remaining drug.	Highly porous nanocellulose absorbing water.	Fails completely if the matrix erodes significantly.
Higuchi	$Q_t = K\_H\sqrt{t}$	Fickian diffusion dominates the process.	Insoluble CNF or BNC hydrogels.	Assumes the matrix geometry does not change over time.
Korsmeyer-Peppas	$Q_t/Q_\infty = K\_KP\ t^n$	Exponential mechanism identifier.	Swelling and relaxing hybrid lignin-cellulose systems.	Only mathematically valid for the first 60% of fractional release. A good fit does not confirm mechanism: Higuchi assumes fixed matrix geometry and fails once swelling or erosion begins, and Hixson–Crowell assumes a uniform shrinking shape that irregular, aggregating lignin particles violate; model choice should follow carrier geometry and dominant transport mechanism before parameters are used to predict dosing.
Hixson-Crowell	$Q_0^{1/3} - Q_t^{1/3} = K\_HC\ t$	Release controlled by particle erosion and shrinking surface area.	Degrading nano-lignin particles.	Assumes a uniform particle shape is strictly maintained during erosion.

Release models are sometimes treated as curve-fitting tools without enough attention to their assumptions. A swelling cellulose hydrogel governed mainly by diffusion behaves differently from an eroding lignin particle. Model choice should reflect that distinction and should be justified before the parameters are used to predict dosing. (Korsmeyer et al., 1983; Hixson & Crowell, 1931; Higuchi, 1963)

Discussion

Manufacturing, Scale-Up, and Translational Challenges

Laboratory methods can produce relatively uniform nano-lignin and CNCs, but pharmaceutical-scale production is more difficult. (Wijaya et al., 2021; Plackett et al., 2014; Sipponen et al., 2018; Anonymous, 2025)

Raw-material variation is a central problem. Lignin and cellulose properties change with plant species, harvest conditions, and pulping method, which affects reproducibility between batches. Several established processes also have substantial resource costs. TEMPO oxidation and antisolvent precipitation use chemical reagents or organic solvents, while ultrasonication requires considerable energy. (Sipponen et al., 2018; Anonymous, 2025; Masruchin et al., 2017; Liu et al., 2020)

Downstream processing adds further constraints. Residual solvents, crosslinkers, and hydrolysis reagents must be removed by dialysis or ultrafiltration, neither of which is easy to operate continuously at large scale. Freeze-drying can improve storage, but particles may aggregate through hydrogen bonding unless an appropriate cryoprotectant is used. Sterilization is another concern because heat or irradiation can change the polymer network and, in turn, the release profile. (Wijaya et al., 2021; Plackett et al., 2014) Specifically, moist-heat autoclaving can hydrolyse and soften cellulose networks, gamma or electron-beam irradiation can crosslink or chain-scission both polymers and shift molecular weight and release, and 0.22 μm sterile filtration is unavailable for particles or gels above the filter cut-off; the chosen sterilization route must be validated against the release specification rather than assumed neutral. Within a Quality-by-Design framework, critical quality attributes (particle size, PDI, zeta potential, encapsulation efficiency, residual reagents, endotoxin, and sterility) should be held within defined ranges by controlling critical process parameters to ensure batch-to-batch consistency during scale-up toward GMP manufacturing.of

Regulatory and Clinical Translation Perspectives

Lignocellulosic nanomedicines do not yet fit neatly within established regulatory categories. The FDA and EMA generally expect a Quality-by-Design (QbD) approach in which critical quality attributes, including particle size, polydispersity, surface charge, and encapsulation efficiency, remain within defined limits during manufacturing. (Wijaya et al., 2021)

Exact molecular uniformity is difficult to establish for carriers obtained from variable natural

sources. Regulatory evaluation may therefore need to rely on defined operating ranges and functional assays rather than a single atomic structure. Standard toxicology protocols are also lacking for high-aspect-ratio CNCs and polyphenolic lignin colloids. Better preclinical models are needed to connect simple buffer-release tests with human pharmacokinetics. (Wijaya et al., 2021; Dong et al., 2012; Anonymous, 2019; Anonymous, 2023c) Figure 8 summarizes the safety, manufacturing, and regulatory decision process.

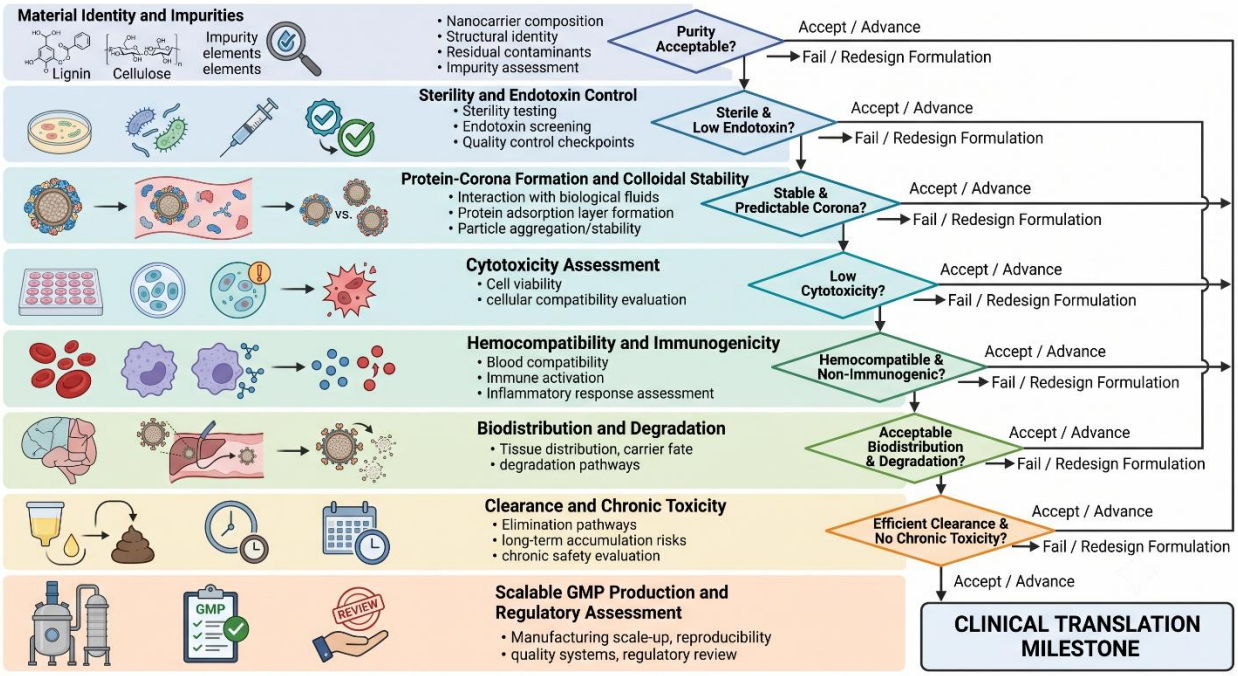

Figure 8. Safety and translation cascade for lignocellulosic nanocarriers. Evaluation proceeds from material identity and impurities through sterility and endotoxin control, protein-corona formation and colloidal stability, cytotoxicity, hemocompatibility and immunogenicity, biodistribution and degradation, clearance and chronic toxicity, and finally scalable good-manufacturing-practice production and regulatory assessment. Decision points indicate acceptance or formulation redesign.

Many studies continue to report new formulations without addressing the standardization needed for manufacturing. Progress toward GMP production will depend more on reproducibility, sterilization, and scalable purification than on small improvements in loading capacity.

Sustainability and Green Nanomedicine Perspective

Lignocellulosic carriers are often described as sustainable because they can use agricultural and forestry residues. That description is incomplete, however, if it considers only the biological origin of the feedstock and not the energy, water, and chemicals used during processing. (Wijaya et al., 2021)

Life-cycle assessments of nanocellulose production have identified substantial environmental costs. Ionic liquids, mineral acids, TEMPO oxidation, mechanical homogenization, and solvent recovery can consume large amounts of energy, water, or reagents. In some processes, these stages offset much of the carbon benefit attributed to the biomass feedstock. (Plackett et al., 2014;

Masruchin et al., 2017; Liu et al., 2020)

Several alternatives may reduce these burdens. Deep eutectic solvents and ammonium persulfate oxidation can lower the impact of nanocellulose isolation, while aerosol flow reactors and spray drying can reduce solvent use in lignin-particle production. A credible assessment of green nanomedicine must compare these processing costs with the purity required for biomedical use. (Anonymous, 2023; Anonymous, 2022c)

Research Gaps

Research on lignocellulosic drug delivery has grown quickly, but several gaps still limit commercialization. Many studies stop after cell-line experiments, leaving little long-term information on pharmacokinetics, biodistribution, or chronic toxicity. Standard nanoparticle assays may also be inadequate for needle-shaped CNCs or chemically variable lignin particles. (Anonymous, 2022a; Dong et al., 2012; Anonymous, 2019; Anonymous, 2023c)

The clearance of cellulose nanoparticles and crosslinked lignin matrices is still poorly defined in humans. At the manufacturing level, precipitation conditions that work in small batches may change under industrial mixing and flow, adding to feedstock variability. Release studies are also commonly performed in static phosphate-buffered saline, which does not reproduce protein-corona formation, enzyme activity, or physiological shear. (Anonymous, 2022a; Dong et al., 2012; Anonymous, 2019; Anonymous, 2023c) In summary, the principal limitations of the current evidence base are: the absence of standardized long-term toxicological and pharmacokinetic data; reliance on non-physiological static-buffer release testing; manufacturing validated only at small scale under variable feedstocks; targeting claims that often reflect passive EPR rather than demonstrated ligand-mediated uptake; and hybrid systems whose synergy is frequently assumed rather than proven by additive controls. These gaps, rather than incremental gains in loading capacity, should define the next stage of research. Table 8 links these gaps to research priorities in toxicology, manufacturing, material science, pharmacology, and regulation. Across these areas, the need is for standardized studies that use physiologically relevant conditions and processes that can be scaled.

Table 8. Research gaps and future research directions

Domain	Identified Research Gap	Proposed Future Direction
Toxicology	Lack of long-term chronic toxicity and clearance data.	Execution of standardized multi-year *in vivo* trials mapping precise hepatic and renal excretion paths.
Manufacturing	Batch-to-batch inconsistency due to raw biomass variability.	Implementation of AI-assisted quality control and advanced fractionation techniques to strictly standardize precursors.
Material Science	Poor redispersion of lyophilized nanoparticles leading to aggregation.	Development of novel, highly biocompatible cryoprotectants specifically tailored for hydrogen-bonding biopolymers.
Pharmacology	Heavy reliance on simple PBS	Utilizing advanced microfluidic organ-on-a-chip models

	buffer *in vitro* release assays.	that accurately simulate physiological fluid dynamics and protein interactions.
Regulation	Absence of unified guidelines for natural polymeric nanoparticles.	Collaborative establishment of Critical Quality Attributes (CQAs) specific to lignocellulosic materials to satisfy FDA/EMA requirements.

Future Research Directions

Future work needs to place more emphasis on translation and less on producing additional proof-of-concept materials. (Wijaya et al., 2021)

Hybrid lignin-cellulose platforms are one practical direction. They could combine mechanical support with antioxidant activity and carry both hydrophilic and hydrophobic drugs. Machine-learning models may also help relate variable biomass chemistry to particle properties, provided they are trained on sufficiently consistent and well-characterized data. (Wijaya et al., 2021)

Adding superparamagnetic iron oxide or gold particles could combine imaging, photothermal treatment, and stimulus-dependent release in one carrier. In parallel, agreed critical quality attributes and life-cycle assessments may make regulatory evaluation more consistent. (Anonymous, 2023b) Figure 9 presents a modular lignin-cellulose platform that combines therapeutic, imaging, manufacturing, and sustainability considerations.nano

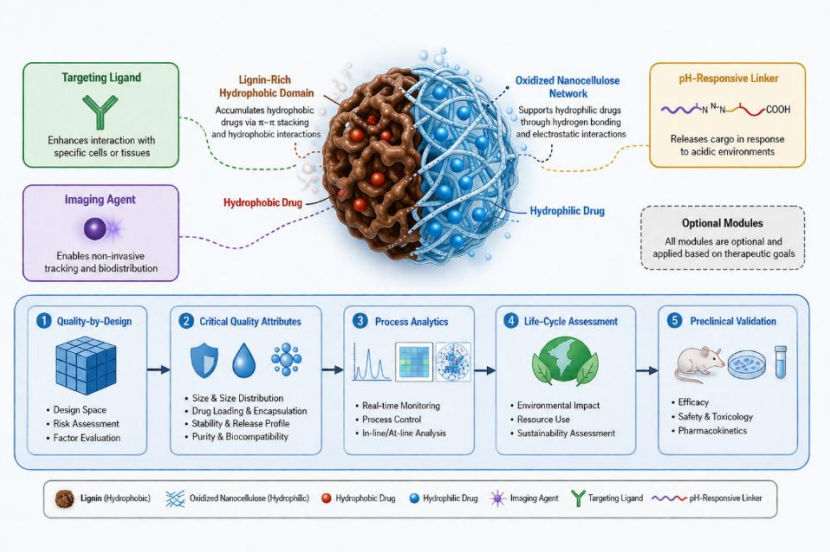

Figure 8. Proposed modular lignin-cellulose hybrid nanocarrier. A lignin-rich hydrophobic domain accommodates a hydrophobic drug, whereas an oxidized nanocellulose network supports a hydrophilic drug. Optional modules include a targeting ligand, imaging agent, and pH-responsive linker, integrated with Quality-by-Design, critical quality attributes, process analytics, life-cycle assessment, and preclinical validation. All modules are conceptual and optional.

Conclusion

Nano-lignin and cellulose-based carriers offer distinct but complementary options for drug delivery. Lignin's aromatic structure and antioxidant activity make it useful for protecting and carrying hydrophobic drugs. Nanocellulose provides mechanical support, adjustable surface chemistry, and generally favorable biocompatibility in the models studied, making it suitable for hydrogels, oral carriers, and wound dressings. (Wijaya et al., 2021; Plackett et al., 2014)

distinct Clinical development is limited by the chemical variability of natural feedstocks and by the requirements of pharmaceutical standardization, scale-up, and sterilization. In vitro results are often encouraging, but long-term evidence on safety, biodistribution, and clearance remains too limited to support routine human use. (Anonymous, 2022a; Dong et al., 2012; Anonymous, 2019; Anonymous, 2023c)

The next stage of research should focus on these practical constraints. Reproducible quality-by-design manufacturing, well-characterized hybrid systems, and life-cycle assessment will be needed alongside efficacy studies. Nano-lignin and nanocellulose should therefore be judged on measurable performance and safety, not simply on their renewable origin. (Wijaya et al., 2021)

Data availability statement

Not applicable. This is a review article and no primary data were generated.

Ethical considerations

The authors avoided data fabrication, falsification, and plagiarism, and any form of misconduct. As this is a narrative review based on published literature, no ethical approval was required.

Conflict of interest

The authors declare no conflict of interest.

Declaration of Generative AI and AI-assisted technologies in the writing process

The authors declare that no generative AI or AI-assisted technologies were used in the writing process of this manuscript beyond basic grammar and spelling checking tools.

CRediT authorship contribution statement

All authors contributed equally to the conceptualization of the article and writing of the original and subsequent drafts.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

Alqahtani, M. S., Alqahtani, A., Al-Thabit, A., Roni, M. A., & Syed, R. (2019). Novel lignin nanoparticles for oral drug delivery. Journal of Materials Chemistry B, 7(28), 4461–4473. https://doi.org/10.1039/C9TB00594C

Auvinen, V.-V., Laurén, P., Shen, B., Isokuortti, J., Durandin, N., Lajunen, T., et al. (2022). Nanoparticle release from anionic nanocellulose hydrogel matrix. Cellulose, 29(18), 9707–9717. https://doi.org/10.1007/s10570-022-04875-1

Auvinen, V.-V., Virtanen, J., Merivaara, A., Virtanen, V., Laurén, P., Tuukkanen, S., et al. (2020). Modulating sustained drug release from nanocellulose hydrogel by adjusting the inner geometry of implantable capsules. Journal of Drug Delivery Science and Technology, 57, 101625. https://doi.org/10.1016/j.jddst.2020.101625

Bacakova, L., Pajorova, J., Bacakova, M., et al. (2019). Versatile application of nanocellulose: From industry to skin tissue engineering and wound healing. Nanomaterials, 9(2), 164. https://doi.org/10.3390/nano9020164

Barbosa, A., Robles, E., Ribeiro, J., Lund, R., Carreño, N., & Labidi, J. (2016). Cellulose nanocrystal membranes as excipients for drug delivery systems. Materials, 9(12), 1002. https://doi.org/10.3390/ma9121002

Berglund, L., Squinca, P., Baş, Y., Zattarin, E., Aili, D., Rakar, J., et al. (2023). Self-assembly of nanocellulose hydrogels mimicking bacterial cellulose for wound dressing applications. Biomacromolecules, 24(5), 2264–2277. https://doi.org/10.1021/acs.biomac.3c00152

Bi, H., Zhang, X., Wang, Q., Yong, Q., Xu, W., Xu, M., et al. (2023). Dynamic reversible disulfide bonds hydrogel of thiolated galactoglucomannan/cellulose nanofibril with self-healing property for protein release. Industrial Crops and Products, 206, 117615. https://doi.org/10.1016/j.indcrop.2023.117615

Chai, Y., Wang, Y., Li, B., Qi, W., Su, R., & He, Z. (2021). Microfluidic synthesis of lignin/chitosan nanoparticles for the pH-responsive delivery of anticancer drugs. Langmuir. https://doi.org/10.1021/acs.langmuir.1c00778

Chen T, He X, Jiang T, Liu W, Li Y, Liu P, Liu Z. Synthesis and drug delivery properties of Ibuprofen-Cellulose nanofibril system. Int J Biol Macromol. 2021 Jul 1;182:931-937. https://doi.org/10.1016/j.ijbiomac.2021.04.096

Controlled synthesis of smaller than 100 nm lignin nanoparticles in a furnace aerosol reactor. (2023). ACS ES&T Engineering. https://doi.org/10.1021/acsestengg.2c00386

Dong, S., Hirani, A. A., Colacino, K. R., Lee, Y. W., & Roman, M. (2012). Cytotoxicity and cellular uptake of cellulose nanocrystals. Nano LIFE, 2(3), 1241006. https://doi.org/10.1142/s1793984412410061

Drug-loading content influences cellular uptake of polymer-coated nanocellulose. (2023). Molecular Pharmaceutics. https://doi.org/10.1021/acs.molpharmaceut.2c00997

Ebadati, A., Ghalandari, B., Hasanzadeh, A., & Karimi, M. (2022). Curcumin/Graphene quantum dot-loaded bacterial nanocellulose platform for drug delivery and wound dressing. Nano, 17(4), 2250021. https://doi.org/10.1142/s1793292022500217

Figueiredo, P., Ferro, C., Kemell, M., et al. (2017). Functionalization of carboxylated lignin nanoparticles for targeted and pH-responsive delivery of anticancer drugs. Nanomedicine, 12(21), 2581–2596. https://doi.org/10.2217/nnm-2017-0219

Figueiredo, P., Lintinen, K., Hirvonen, J. T., Kostiainen, M. A., & Santos, H. A. (2018). Development of a novel lignin-based polymeric nanoparticle platform for efficient delivery of anticancer drugs. ACS Biomaterials Science & Engineering. https://doi.org/10.1021/acsbiomaterials.8b00260

Formation of homogeneous lignin nanoparticles from industrial kraft lignin via fractionation combined with antisolvent precipitation. (2025). Biomacromolecules. https://doi.org/10.1021/acs.biomac.4c01604

Gupta, A., Briffa, S., Swingler, S., et al. (2020). Synthesis of silver nanoparticles using curcumin-cyclodextrins loaded into bacterial cellulose-based hydrogels for wound dressing applications. Biomacromolecules, 21(5), 1802–1811. https://doi.org/10.1021/acs.biomac.9b01724

Higuchi, T. (1963). Mechanism of sustained-action medication: Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. Journal of Pharmaceutical Sciences, 52(12), 1145–1149. https://doi.org/10.1002/jps.2600521210

Highly functional materials based on nano-lignin, lignin, and lignin/silica hybrid capped silver nanoparticles with antibacterial activities. (2022). Biomacromolecules. https://doi.org/10.1021/acs.biomac.1c01250

Hixson, A. W., & Crowell, J. H. (1931). Dependence of reaction velocity upon surface and agitation. Industrial & Engineering Chemistry, 23(8), 923–931. https://doi.org/10.1021/ie50260a018

In vitro and in vivo evaluation of drug-encapsulated lignin nanoparticles for release control. (2022). ACS

Sustainable Chemistry & Engineering. https://doi.org/10.1021/acssuschemeng.1c08529

Jeong, D. I., Kim, S., Kim, M.-H., Yoon, I.-S., Lee, S.-H., Kim, D.-D., et al. (2022). Donepezil hydrochloride-reinforced cellulose nanocrystal-aggregated gel structure for long-acting drug delivery. Carbohydrate Polymers, 296, 119887. https://doi.org/10.1016/j.carbpol.2022.119887

Kim, Y. M., Lee, Y. S., Kim, T., Yang, K., Nam, K., Choe, D., et al. (2020). Cationic cellulose nanocrystals complexed with polymeric siRNA for efficient anticancer drug delivery. Carbohydrate Polymers, 247, 116684. https://doi.org/10.1016/j.carbpol.2020.116684

Korsmeyer, R. W., Gurny, R., Doelker, E., Buri, P., & Peppas, N. A. (1983). Mechanisms of solute release from porous hydrophilic polymers. International Journal of Pharmaceutics, 15(1), 25–35. https://doi.org/10.1016/0378-5173(83)90064-9

Kumar, R., & Chauhan, S. (2022). Cellulose nanocrystals based delivery vehicles for anticancer agent curcumin. International Journal of Biological Macromolecules, 221, 842–864. https://doi.org/10.1016/j.ijbiomac.2022.09.077

Lasopha, P., & Lasopha, S. (2024). Development of bacterial cellulose herbal wound dressing. Trends in Sciences, 21(2), 7375. https://doi.org/10.48048/tis.2024.7375

Li, Y., Wang, C., Luan, Y., Liu, W., Chen, T., Liu, P., et al. (2021). Preparation of pH-responsive cellulose nanofibril/sodium alginate based hydrogels for drug release. Journal of Applied Polymer Science, 139(7), 51647. https://doi.org/10.1002/app.51647

Lignocellulosic-based nanoparticles with photoluminescent properties for bioimaging. (2023). ACS Applied Materials & Interfaces. https://doi.org/10.1021/acsami.3c05248

Lipase-responsive lignin composite nanoparticles for the delivery of insoluble bioactives. (2024). Langmuir. https://doi.org/10.1021/acs.langmuir.4c00856

Liu, Y., Fan, Q., Huo, Y., Liu, C., Li, B., & Li, Y. (2020). Construction of a mesoporous polydopamine@GO/cellulose nanofibril composite hydrogel with an encapsulation structure for controllable drug release and toxicity shielding. ACS Applied Materials & Interfaces, 12(51), 57410–57420. https://doi.org/10.1021/acsami.0c15465

Machado, T. O., Beckers, S. J., Fischer, J., et al. (2020). Bio-based lignin nanocarriers loaded with fungicides as a versatile platform for drug delivery in plants. Biomacromolecules, 21(7), 2755–2763. https://doi.org/10.1021/acs.biomac.0c00487

Madanhire, T., Poswayo, O., Ngalo, B., Alven, S., & Magwa, N. (2026). Bacterial cellulose-based materials for drug delivery in wound dressing applications. Journal of Drug Delivery Science and Technology, 120, 108275. https://doi.org/10.1016/j.jddst.2026.108275

Masruchin, N., Park, B.-D., & Causin, V. (2017). Dual-responsive composite hydrogels based on TEMPO-oxidized cellulose nanofibril and poly(N-isopropylacrylamide) for model drug release. Cellulose, 25(1), 485–502. https://doi.org/10.1007/s10570-017-1585-2

Mo, M., Wu, C., & Chen, Y. (2025). Bacterial cellulose-based superabsorbent hydrogel for wet wound dressing. Molecules, 30(3), 737. https://doi.org/10.3390/molecules30030737

Moritz, S., Wiegand, C., Wesarg, F., Hessler, N., Müller, F. A., Kralisch, D., et al. (2014). Active wound dressings based on bacterial nanocellulose as drug delivery system for octenidine. International Journal of Pharmaceutics, 471(1–2), 45–55. https://doi.org/10.1016/j.ijpharm.2014.04.062

Munawaroh, H. S. H., Anwar, B., Yuliani, G., Murni, I. C., Arindita, N. P. Y., Maulidah, G. S., et al. (2023). Bacterial cellulose nanocrystal as drug delivery system for overcoming the biological barrier of cyano-phycocyanin: A biomedical application of microbial product. Bioengineered, 14(1), 2252226. https://doi.org/10.1080/21655979.2023.2252226

Nanocellulose by ammonium persulfate oxidation: An alternative to TEMPO-mediated oxidation. (2022). ACS Sustainable Chemistry & Engineering. https://doi.org/10.1021/acssuschemeng.1c07814

Ndong Ntoutoume, G. M. A., Granet, R., Mbakidi, J. P., Brégier, F., Léger, D. Y., Fidanzi-Dugas, C., et al. (2016). Development of curcumin–cyclodextrin/cellulose nanocrystals complexes: New anticancer drug delivery systems. Bioorganic & Medicinal Chemistry Letters, 26(3), 941–945. https://doi.org/10.1016/j.bmcl.2015.12.060

Patel, D. K., Dutta, S. D., Ganguly, K., & Lim, K.-T. (2021). Multifunctional bioactive chitosan/cellulose nanocrystal scaffolds eradicate bacterial growth and sustain drug delivery. International Journal of Biological Macromolecules, 170, 178–188. https://doi.org/10.1016/j.ijbiomac.2020.12.145

Plackett, D., Letchford, K., Jackson, J., & Burt, H. (2014). A review of nanocellulose as a novel vehicle for drug delivery. Nordic Pulp & Paper Research Journal, 29(1), 105–118. https://doi.org/10.3183/NPPRJ-2014-29-01-p105-118

Plappert, S. F., Liebner, F., Konnerth, J., & Nedelec, J. M. (2019). Anisotropic nanocellulose gel-membranes for drug delivery: Tailoring structure and interface by sequential periodate–chlorite oxidation. Carbohydrate Polymers, 226, 115306. https://doi.org/10.1016/j.carbpol.2019.115306

Rojewska, A., Karewicz, A., Karnas, K., et al. (2020). Pioglitazone-loaded nanostructured hybrid material for skin ulcer treatment. Materials, 13(9), 2050. https://doi.org/10.3390/ma13092050

Seo, J.-H., Lee, S. Y., Hwang, C. R., Yang, M., Lee, J., Lee, S.-H., et al. (2020). Multi-layered cellulose nanocrystal system for CD44 receptor-positive tumor-targeted anticancer drug delivery. International Journal of Biological Macromolecules, 162, 798–809. https://doi.org/10.1016/j.ijbiomac.2020.06.193

Shi, X., Chen, Z., He, Y., Lu, Q., Chen, R., Zhao, C., et al. (2022). Dual light-responsive cellulose nanofibril-based in situ hydrogel for drug-resistant bacteria infected wound healing. Carbohydrate Polymers, 297, 120042. https://doi.org/10.1016/j.carbpol.2022.120042

Silver-functionalized bacterial cellulose as antibacterial membrane for wound-healing applications. (2017). ACS Omega, 2(7), 3632–3639. https://doi.org/10.1021/acsomega.7b00442

Sipponen, M. H., Lange, H., Ago, M., & Crestini, C. (2018). Understanding lignin aggregation processes. A case study: Budesonide entrapment and stimuli-controlled release from lignin nanoparticles. ACS Sustainable Chemistry & Engineering, 6(7), 9342–9351. https://doi.org/10.1021/acssuschemeng.8b01650

Tissue response and biodistribution of injectable cellulose nanocrystal composite hydrogels. (2019). ACS Biomaterials Science & Engineering. https://doi.org/10.1021/acsbiomaterials.9b00522

Tong, W. Y., bin Abdullah, A. Y. K., binti Rozman, N. A. S., bin Wahid, M. I. A., Hossain, M. S., Ring, L. C., et al. (2017). Antimicrobial wound dressing film utilizing cellulose nanocrystal as drug delivery system for curcumin. Cellulose, 25(1), 631–638. https://doi.org/10.1007/s10570-017-1562-9

Wang, H., & Roman, M. (2011). Formation and properties of chitosan−cellulose nanocrystal polyelectrolyte−macroion complexes for drug delivery applications. Biomacromolecules, 12(5), 1585–1593. https://doi.org/10.1021/bm101584c

Wijaya, C. J., Ismadji, S., & Gunawan, S. (2021). A review of lignocellulosic-derived nanoparticles for drug delivery applications: Lignin nanoparticles, xylan nanoparticles, and cellulose nanocrystals. Molecules, 26(3), 676. https://doi.org/10.3390/molecules26030676

Won, S. Y., Rao, K. M., & Han, S. S. (2025). Quaternized hydroxyethyl cellulose/tannic acid-impregnated bacterial cellulose hydrogels for wound dressing applications. Applied Surface Science, 713, 164312. https://doi.org/10.1016/j.apsusc.2025.164312

Wu, X., Huang, J., Zhou, Y., Jing, M., Li, Y., Liu, Z., et al. (2026). Cellulose nanofibril-directed interfacial assembly of electroactive hydrogel dressings for diabetic wound repair. Industrial Crops and Products, 249, 123804. https://doi.org/10.1016/j.indcrop.2026.123804

Xu, Q., Ji, Y., Sun, Q., Fu, Y., Xu, Y., & Jin, L. (2019). Fabrication of cellulose nanocrystal/chitosan hydrogel for controlled drug release. Nanomaterials, 9(2), 253. https://doi.org/10.3390/nano9020253

Yusefi, M., Soon, M. L.-K., Teow, S.-Y., Monchouguy, E. I., Neerooa, B. N. H. M., Izadiyan, Z., et al. (2022). Fabrication of cellulose nanocrystals as potential anticancer drug delivery systems for colorectal cancer treatment. International Journal of Biological Macromolecules, 199, 372–385. https://doi.org/10.1016/j.ijbiomac.2021.12.189

Zhao, J., Lu, C., He, X., Zhang, X., Zhang, W., & Zhang, X. (2015). Polyethylenimine-grafted cellulose nanofibril aerogels as versatile vehicles for drug delivery. ACS Applied Materials & Interfaces, 7(4), 2607–2615. https://doi.org/10.1021/am507601m

Zheng, D., Deng, Y., Xia, Y., Nan, Y., Peng, M., Wang, X., et al. (2019). Fabrication and performance of a spherical cellulose nanocrystal-based hydrophobic drug delivery vehicle using rubber wood. BioResources, 14(4), 7763–7774. https://doi.org/10.15376/biores.14.4.7763-7774

Zhou, Y., Han, Y., Li, G., Yang, S., & Chu, F. (2019). Lignin-based hollow nanoparticles for controlled drug delivery: Grafting preparation using β-cyclodextrin/enzymatic-hydrolysis lignin. Nanomaterials, 9(7), 997. https://doi.org/10.3390/nano9070997

Zhou, Y., Han, Y., Li, G., Yang, S., Xiong, F., & Chu, F. (2019). Preparation of targeted lignin-based hollow nanoparticles for the delivery of doxorubicin. Nanomaterials, 9(2), 188. https://doi.org/10.3390/nano9020188