Advances in Plant-Derived Cellulose Nanomaterials for Biomedical Applications: Processing Technologies, Functional Properties, and Drug Delivery Potential

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Abstract

Plant-derived cellulose nanomaterials, principally cellulose nanocrystals (CNCs) and cellulose nanofibrils (CNFs), combine high stiffness, large specific surface area, abundant surface hydroxyl groups and low intrinsic toxicity, and are being developed for drug delivery, wound care and tissue engineering. Their biological performance, however, depends strongly on how they are produced, and the conditions needed to translate them into approved products remain poorly integrated in the literature. This advances review examines how processing technologies shape the functional properties and drug delivery potential of plant nanocellulose, and what manufacturing, safety, regulatory and health system conditions govern its clinical translation. An integrative review design was adopted. Peer-reviewed literature published between 2005 and 2021 was identified through structured searches of Web of Science, Scopus, PubMed and Google Scholar, supplemented by backward and forward citation tracking. Eligible sources were appraised and synthesised thematically, and the resulting themes were used to build a conceptual model. The synthesis shows that feedstock and processing choices (acid hydrolysis, TEMPO-mediated oxidation, enzymatic and mechanical fibrillation, greener solvent routes, drying and sterilisation) determine particle dimensions, crystallinity, surface chemistry and purity. These attributes govern rheology, gelation, drug binding, biocompatibility and degradability, and therefore release behaviour. Oral sustained-release matrices and topical wound dressings are the most mature applications, injectable hydrogels are advancing, and targeted systemic nanocarriers remain largely preclinical. A Process-Structure-Function-Translation (PSFT) model is proposed, comprising five linked stages, an enabling layer of quality, safety, regulatory, supply chain, health system and workforce conditions, and a feedback loop, expressed as six testable propositions. The model provides researchers, manufacturers and regulators with a structured basis for specifying critical material attributes and prioritising evidence. The review is limited by its non-systematic design, English-language scope and 2021 cut-off, and the model awaits empirical validation. Priorities include standardised reporting, long-term biodistribution and degradation studies, residue-based biomedical-grade production and clinical trials.

Keywords: nanocellulose; cellulose nanocrystals; cellulose nanofibrils; TEMPO oxidation; hydrogels; drug delivery; biocompatibility; agricultural residues; clinical translation; conceptual model

DOI: 10.18091/ijsts.v5i1-2.004

1. Introduction

Cellulose is a linear homopolymer of β-(1→4)-linked D-anhydroglucopyranose units and constitutes the main structural component of plant cell walls, where it accounts for roughly 35 to 50% of lignocellulosic dry mass. Annual natural production has been estimated in the order of 10^{11} to 10^{12} tonnes, making cellulose a practically inexhaustible renewable resource (Habibi et al., 2010; Klemm et al., 2011). Within the cell wall, cellulose chains are synthesised by membrane-bound cellulose synthase complexes and coalesce, through extensive intra- and intermolecular hydrogen bonding, into elementary fibrils approximately 3 to 5 nm wide. These elementary fibrils aggregate into microfibril bundles embedded in a matrix of hemicelluloses, pectins and lignin, producing a hierarchical composite of remarkable strength (Klemm et al., 2005).

When this hierarchy is deconstructed to the nanoscale, the resulting materials retain the stiffness of crystalline cellulose (an axial elastic modulus of approximately 110 to 220 GPa has been estimated for crystalline domains) while exposing an enormous, chemically addressable surface (Moon et al., 2011). The term "nanocellulose" is now used collectively for cellulose materials with at least one dimension below 100 nm. Three families are generally recognised: cellulose nanocrystals (CNCs, also called cellulose nanowhiskers), cellulose nanofibrils (CNFs, also called microfibrillated or nanofibrillated cellulose) and bacterial cellulose (BC), which is produced bottom-up by microorganisms such as Komagataeibacter xylinus (Dufresne, 2013; Klemm et al., 2011). Plant-derived CNCs and CNFs are the focus of this review because they can be produced at scale from wood pulp, agricultural residues and other low-cost biomass, and because several industrial producers now supply them in tonne quantities.

Biomedical interest in plant nanocellulose arises from a convergence of attributes. The materials are derived from a polymer that has a long record of safe use in pharmaceutical excipients (microcrystalline cellulose and cellulose ethers), they form hydrogels at low solids content, they can be shaped into films, foams, aerogels and printed scaffolds, and their surfaces can be functionalised to bind drugs, peptides, nucleic acids or targeting ligands (Jorfi & Foster, 2015; Lin & Dufresne, 2014). At the same time, their high aspect ratio, poor biodegradability in human tissues and process-dependent impurities raise legitimate questions about safety that must be answered before clinical adoption.

Several reviews have surveyed nanocellulose production and properties (Habibi et al., 2010; Kargarzadeh et al., 2017; Klemm et al., 2011; Moon et al., 2011) or its general biomedical potential (Curvello et al., 2019; Jorfi & Foster, 2015; Lin & Dufresne, 2014), and others have

focused on drug delivery (Plackett et al., 2014; Seabra et al., 2018) or hydrogels (De France et al., 2017; Du et al., 2019). Three gaps nevertheless remain. First, processing choices are seldom linked systematically to the biological and delivery outcomes they produce, so that studies of the same nominal material are difficult to compare. Second, the conditions that govern translation, such as manufacturing quality, occupational safety, regulatory science, supply chains and health system capacity, are rarely integrated into reviews of nanocellulose biomedicine, even though they determine whether laboratory advances reach patients. This gap is especially relevant to emerging economies in sub-Saharan Africa that hold abundant agricultural residues but limited pharmaceutical manufacturing capacity. Third, there is no conceptual model that connects these elements and generates testable propositions.

This review addresses these gaps through three research questions:

- RQ1: How do feedstock and processing technologies determine the structural attributes and functional properties of plant-derived nanocellulose relevant to biomedicine?
- RQ2: What is the current drug delivery potential of plant nanocellulose across dosage forms and routes of administration, and how mature is the supporting evidence?
- RQ3: Which manufacturing, safety, regulatory, supply chain and health system conditions enable or constrain clinical translation?

The objectives are to synthesise the literature published up to 2021 on these questions, to develop a conceptual model that integrates them, and to derive implications and a research agenda. Section 2 describes the research method. Section 3 presents the results and discussion, comprising the literature synthesis, the conceptual model, the discussion of findings and their implications. Section 4 concludes the paper and sets out its limitations and directions for future research.

2. Research Method

2.1 Review design

An integrative literature review design was adopted because the research questions span experimental materials science, preclinical pharmacology and conceptual work on manufacturing, regulation and health systems, which cannot be pooled statistically. Integrative reviews allow diverse study designs to be combined in a structured way and are well suited to building new conceptual frameworks (Snyder, 2019; Torraco, 2005; Whittemore & Knafl, 2005). Reporting of the search and selection process was informed by the principles of the PRISMA 2020 statement, although a full systematic review protocol was not registered (Page et al., 2021).

2.2 Search strategy

Two complementary search streams were used. The core stream addressed nanocellulose science and biomedicine and was conducted in Web of Science Core Collection, Scopus, PubMed and Google Scholar. The search string combined material terms ("nanocellulose" OR "cellulose nanocrystal*" OR "cellulose nanofib*" OR "nanofibrillated cellulose" OR "microfibrillated

cellulose" OR "TEMPO-oxidized cellulose") with application terms ("drug delivery" OR "controlled release" OR "hydrogel" OR "wound" OR "tissue engineering" OR "bioink" OR "biocompatib*" OR "toxicity"). The translational stream addressed the enabling conditions identified during the core synthesis, namely agricultural residue valorisation, manufacturing quality and process equipment, occupational and environmental safety, pharmaceutical regulatory science, supply chains, health system and laboratory infrastructure, and workforce development, with an emphasis on sub-Saharan African and other emerging-economy contexts. Searches covered January 2005 to December 2021 and were supplemented by backward and forward citation tracking of key reviews.

2.3 Eligibility criteria

Sources were included if they (i) were peer-reviewed journal articles, reviews or conference papers published between 2005 and 2021; (ii) were written in English; and (iii) for the core stream, reported the production, characterisation, biological evaluation or biomedical application of plant-derived CNCs or CNFs, or, for the translational stream, addressed a condition relevant to the manufacture, safety, regulation, distribution or clinical uptake of biomaterials or medicines. Sources were excluded if they dealt only with bacterial or algal cellulose without comparison to plant material, addressed non-biomedical applications without transferable insight, lacked basic material characterisation, or were patents, theses and other grey literature.

2.4 Screening and quality appraisal

Titles and abstracts were screened against the eligibility criteria, followed by full-text assessment. Experimental studies were appraised for the adequacy of material characterisation (dimensions, crystallinity, surface chemistry and charge), the use of appropriate controls, consideration of endotoxin and assay interference, and the relevance of the biological model. Reviews and conceptual papers were appraised for relevance, transparency of argument and consistency with the wider evidence. Appraisal was used to weight the contribution of sources to the synthesis rather than to exclude them, so that the breadth of the field could be represented.

2.5 Data extraction, synthesis and model development

For each core source, data were extracted on feedstock, processing route, particle dimensions, surface chemistry, crystallinity, formulation type, payload, release behaviour and biological outcomes. For translational sources, the condition addressed, the setting and the mechanism proposed were recorded. Data were synthesised using thematic analysis, with codes grouped iteratively into themes (Braun & Clarke, 2006). These themes were then organised along the value chain from biomass to patient and used to build the conceptual model following the procedure for developing conceptual frameworks described by Jabareen, in which concepts are identified, deconstructed, integrated and synthesised into a coherent whole (Jabareen, 2009). Table 1 summarises the review protocol.

Table 1. Summary of the review protocol.

Element	Description
Design	Integrative literature review informed by PRISMA 2020 principles
Databases	Web of Science Core Collection, Scopus, PubMed, Google Scholar; citation tracking
Period	January 2005 to December 2021
Language	English
Core stream	Plant-derived CNC and CNF production, properties, biocompatibility and biomedical applications
Translational stream	Agricultural residues, manufacturing quality, safety, regulation, supply chains, health systems, workforce
Exclusions	Bacterial or algal cellulose only; non-transferable non-biomedical uses; inadequate characterisation; grey literature
Synthesis	Thematic analysis; themes mapped to value chain stages
Output	Process-Structure-Function-Translation (PSFT) conceptual model with six propositions

3. Results and Discussion

This section first presents the results of the literature synthesis in five themes that follow the value chain from biomass to biomedical application: processing technologies, structure and functional properties, biocompatibility and safety, drug delivery and tissue engineering (Sections 3.1 to 3.5). It then introduces the conceptual model derived from the synthesis (Section 3.6), discusses the principal findings, barriers and contribution of the review (Sections 3.7 to 3.9) and sets out the implications (Section 3.10).

3.1 Processing Technologies for Plant-Derived Nanocellulose

3.1.1 Feedstocks and pretreatment

Wood pulps (softwood and hardwood kraft or sulfite pulps) remain the dominant commercial feedstock because they are already delignified and available in consistent grades. However, a large body of work has examined non-wood sources including cotton linters, sugarcane bagasse, wheat and rice straw, corn stover, banana and pineapple leaf fibres, hemp, flax, kenaf, oil palm empty fruit bunches, cassava bagasse and coconut husk (Kargarzadeh et al., 2017; Trache et al., 2017). These residues offer cost and sustainability benefits and, in regions with large agricultural sectors such as sub-Saharan Africa and South and Southeast Asia, a route to valorising waste streams. Feedstock choice affects cellulose crystallinity, the polymorph distribution (Iα versus

Iβ), the length of native microfibrils and the content of residual hemicellulose and lignin, all of which carry through to the final nanomaterial (Trache et al., 2017).

Non-wood feedstocks generally require purification before nanocellulose isolation. Typical sequences combine alkaline treatment (for example 2 to 5% NaOH at elevated temperature) to remove hemicelluloses and waxes with bleaching steps using sodium chlorite or hydrogen peroxide to remove lignin. For biomedical use, these steps must be followed by thorough washing, because residual oxidants, salts, lignin fragments and microbial endotoxins can confound biological assays and compromise safety (Jorfi & Foster, 2015; Nordli et al., 2016).

3.1.2 Agricultural residues, circular economy and regional value chains

The valorisation of agricultural residues into nanocellulose aligns with broader agricultural development and sustainability agendas. Policy and economic analyses emphasise that aligning agricultural policy with national sustainable development priorities, and using data-driven policy models, can improve resource efficiency and food system performance (Michael & Ogunsola, 2021a, 2021c). Digital agriculture tools and climate-smart practices are reshaping production systems and household incomes (Michael & Ogunsola, 2021b, 2021d), and linking West African agricultural value chains to household economic stability is a recognised development goal (Jones & Ominyi, 2021). Converting crop and processing residues into higher-value biomaterials offers one route to such value addition. Uptake of new value-addition technologies in rural economies depends on extension services, access to finance and entrepreneurial competencies (Michael & Ogunsola, 2019a, 2019b, 2021e), and on removing barriers that limit the participation of women in African business leadership and enterprise (Ukadike & Ibeh, 2020).

Cassava (Manihot esculenta) peels and other farm residues are a particularly relevant example for West Africa. Large volumes of these residues are currently used mainly as low-value animal feed, and their acceptability and physiological effects when fed with Gmelina arborea leaves have been characterised in sheep (Aye & Tawose, 2015, 2016). These compositional and utilisation data provide a baseline for assessing residues that could instead be directed to nanocellulose production. Agricultural plant extracts have also been applied as green corrosion inhibitors (Atta et al., 2018), and locally sourced building materials have been evaluated for sustainable housing (Nwafor et al., 2019), indicating a growing regional base of expertise in agro-derived materials.

3.1.3 Cellulose nanocrystals by acid hydrolysis

CNCs are classically produced by controlled hydrolysis of purified cellulose with concentrated mineral acid, most commonly 60 to 65 wt% sulfuric acid at 40 to 50 °C for 30 to 60 min (Habibi et al., 2010; Moon et al., 2011). The acid preferentially attacks the less ordered, more accessible regions of the microfibrils, leaving rod-like crystallites. For wood and cotton sources, typical CNCs are 3 to 10 nm wide and 100 to 300 nm long, with crystallinity indices between about 70 and 90% (Moon et al., 2011). Tunicate and algal CNCs are longer but are not plant derived in the strict sense and are less relevant to scalable biomedical supply.

Sulfuric acid hydrolysis esterifies a fraction of surface hydroxyl groups to sulfate half-esters, conferring a negative surface charge (typically 0.1 to 0.3 mmol g^{-1}) that stabilises aqueous colloidal suspensions through electrostatic repulsion. This charge also enables the chiral nematic self-assembly that gives CNC films their characteristic iridescence (Habibi et al., 2010). The drawbacks are reduced thermal stability, a low yield (often 30 to 50%), large volumes of acidic effluent and the presence of sulfate groups that may interact with biological systems. Hydrochloric acid hydrolysis yields uncharged CNCs with higher thermal stability but poor colloidal stability, while phosphoric acid produces phosphorylated CNCs with better thermal stability and potential for bone-related applications (Camarero Espinosa et al., 2013). Organic acids (for example oxalic, maleic or formic acid), sometimes combined with mechanical treatment, have been proposed as recyclable and less corrosive alternatives that introduce carboxyl groups during hydrolysis.

Oxidative routes offer another path. Ammonium persulfate oxidation can produce carboxylated CNCs directly from lignocellulosic materials in a single step, and sequential periodate/chlorite oxidation yields dicarboxylated nanocrystals whose charge can be tuned over a wide range. These approaches are attractive for drug delivery because carboxyl groups are convenient handles for amide coupling of drugs and ligands.

3.1.4 Cellulose nanofibrils by mechanical fibrillation

CNFs are produced by mechanically delaminating pulp fibres into long, flexible fibril networks. Common equipment includes high-pressure homogenisers, microfluidisers, supermasscolloider (ultrafine friction) grinders, twin-screw extruders and high-intensity ultrasonicators (Kargarzadeh et al., 2017; Siró & Plackett, 2010). CNFs are typically 5 to 50 nm wide and several micrometres long, containing both crystalline and disordered segments; their very high aspect ratio produces entangled networks that form gels at solids contents below 1 wt%.

Purely mechanical fibrillation is energy intensive, historically requiring 20,000 to 30,000 kWh per tonne, and early processes suffered from clogging of homogenisers. The introduction of pretreatments reduced energy demand by an order of magnitude and improved fibril uniformity (Siró & Plackett, 2010). Mechanical-only CNFs nonetheless retain value where minimal chemical modification is desired, for example in certain regulatory contexts.

3.1.5 Chemical and enzymatic pretreatments

The most influential pretreatment has been 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO)-mediated oxidation, developed by Isogai, Saito and co-workers (Isogai et al., 2011; Saito et al., 2007). In the TEMPO/NaBr/NaClO system at pH 10, primary C6 hydroxyl groups on microfibril surfaces are selectively converted to carboxylate groups. The introduced charge (up to approximately 1.5 to 1.7 mmol g^{-1}) generates strong electrostatic repulsion between fibrils, so that gentle mechanical treatment produces individualised fibrils of about 3 to 4 nm width with high transparency. TEMPO-oxidised CNFs (TOCNFs) are now among the most widely studied nanocelluloses for drug delivery because their carboxylates can bind cationic drugs and metal

ions, crosslink with multivalent cations to form hydrogels and serve as attachment points for covalent conjugation. A neutral variant, TEMPO/NaClO/$NaClO_2$ oxidation at pH 4.8 to 6.8, avoids the depolymerisation and aldehyde formation associated with the alkaline system (Isogai et al., 2011).

Carboxymethylation, quaternisation (introducing cationic trimethylammonium groups), phosphorylation and sulfoethylation provide alternative charged surfaces. Cationic CNFs are of particular interest for binding anionic drugs and nucleic acids and have shown intrinsic antimicrobial activity. Enzymatic pretreatment with endoglucanases offers a milder, chemical-free route that cleaves disordered regions and loosens fibre structure; combined with refining and homogenisation, it underpins several commercial processes and generates CNFs without introduced surface charge (Siró & Plackett, 2010).

3.1.6 Emerging and greener processing routes

Concern over the environmental footprint of acid and oxidant use has stimulated research into alternative solvents and media. Deep eutectic solvents (DESs), for example mixtures of choline chloride with urea, oxalic acid or lactic acid, can swell and partially esterify or cationise cellulose and act as recyclable pretreatment media before fibrillation. Ionic liquids such as 1-butyl-3-methylimidazolium salts can produce CNCs under controlled conditions, although cost and residual solvent removal are concerns for biomedical grades. Subcritical water, steam explosion, ball milling and cryocrushing have also been explored, often in combination (Abitbol et al., 2016; Kargarzadeh et al., 2017). For biomedical use, any new route should be judged not only on yield and energy but also on the ease of removing process residues and on reproducibility of surface chemistry.

3.1.7 Drying, redispersion and sterilisation

Nanocellulose is usually produced as dilute aqueous suspensions, and drying causes irreversible aggregation (hornification) through hydrogen bonding between fibrils. Spray drying, freeze drying and supercritical CO_2 drying each produce different morphologies, from microparticles to highly porous aerogels. Additives such as sugars, carboxymethyl cellulose or surface charge introduction improve redispersibility (De France et al., 2017). Sterilisation is a frequently neglected step: autoclaving can reduce viscosity and cause yellowing, gamma irradiation causes chain scission, and ethylene oxide leaves residues. Studies on CNF hydrogels indicate that autoclaving and gamma sterilisation alter rheology to differing degrees, so the chosen method must be validated for each formulation (Nordli et al., 2016). Endotoxin removal deserves specific emphasis because plant and microbial contaminants introduced during pulping can produce false-positive inflammatory responses.

3.1.8 Scale-up, quality management and process equipment

Translating laboratory isolation protocols into reproducible biomedical-grade production is a manufacturing and quality management challenge as much as a chemical one. Lean Six Sigma

frameworks adapted for resource-constrained enterprises, standard operating procedures that act as change infrastructure, and digital transformation of operations through automation and analytics all support consistent output (Agboada et al., 2018, 2019; Ambali et al., 2021). In pharmaceutical manufacturing specifically, risk-based decision-making in good manufacturing practice (GMP) environments and digital transformation of production are central to product quality (Aneke & Adesemoye, 2020; Obukadata et al., 2021a), and reliability engineering and failure analysis methods help prevent process deviations in complex engineered systems (Gideon et al., 2019).

Process equipment deserves particular attention. Concentrated acid hydrolysis is highly corrosive, and corrosion management and material selection strategies developed for aggressive industrial environments are directly relevant to reactor and piping design (Atta et al., 2020; Obetta et al., 2020). High-pressure homogenisers and microfluidisers are pressure equipment whose integrity can be managed through risk-based and non-intrusive inspection, reliability-centred maintenance and risk-based process engineering (Asibor & Isong, 2019; Obetta, 2018, 2020; Obetta et al., 2021). Moving from reactive to predictive maintenance and condition monitoring reduces unplanned downtime in such equipment (Adaramola et al., 2018; Sunday et al., 2020).

Energy demand, particularly for mechanical fibrillation and drying, is a major contributor to cost and environmental impact. Integrating solar power into small-scale manufacturing and optimising load distribution in hybrid solar installations can reduce energy costs for processing facilities in developing economies (Sunday & Omoegun, 2018, 2019). Smart solar microgrids that balance technical performance with affordability, statistical models of solar radiation for planning, interpretable machine learning for early failure prediction in renewable assets, and wind power forecasting all support reliable renewable supply (Komi, 2021; Komi & Adamolekun, 2021; Komi & Adeniji, 2020; Odejobi & Ahmed, 2018). Programmatic strategies for large-scale solar integration, peer-to-peer renewable energy trading and hydrogen as a secondary energy carrier offer further options for decarbonising production (Shittu et al., 2019, 2021; Yeboah & Ike, 2020).

Table 2. Comparison of principal plant-derived nanocellulose types and their typical processing routes.

Parameter	**CNC (H_2SO_4)**	**TEMPO-oxidised CNF**	**Mechanical / enzymatic CNF**
Morphology	Rigid rods	Individualised flexible fibrils	Branched fibril bundles
Width	3 to 10 nm	3 to 5 nm	10 to 50 nm (broad)
Length	100 to 300 nm	0.5 to several μm	1 to several μm

Parameter	CNC (H_2SO_4)	TEMPO-oxidised CNF	Mechanical / enzymatic CNF
Crystallinity	70 to 90%	60 to 75%	50 to 70%
Surface charge	Sulfate half-esters, 0.1 to 0.3 mmol/g	Carboxylate, up to ~1.7 mmol/g	Low or none
Gelation	Only at high solids or with additives	Strong gels below 1 wt%; ion-crosslinkable	Gels at 1 to 2 wt%
Key biomedical uses	Nanocarriers, reinforcement, Pickering emulsions	Injectable gels, drug binding, films, inks	Excipients, wound dressings, cell culture gels
Main limitations	Low yield, acid effluent, lower thermal stability	Oxidant residues, cost of TEMPO	Energy demand, heterogeneity

3.2 Structure and Functional Properties

3.2.1 Mechanical properties and reinforcement

The high axial stiffness of crystalline cellulose and the percolating networks formed by high-aspect-ratio particles make nanocellulose an effective reinforcing phase. Addition of a few weight percent of CNCs to polymers such as poly(vinyl alcohol), alginate, gelatin, chitosan or polycaprolactone can raise modulus and strength substantially, a property exploited in scaffolds and wound dressings (Lin & Dufresne, 2014; Moon et al., 2011). Neat CNF films ("nanopaper") reach tensile strengths of 200 to 300 MPa, and their low porosity yields excellent oxygen barrier properties relevant to protective coatings and packaging of sensitive pharmaceuticals (Lavoine et al., 2012).

3.2.2 Rheology and gel formation

CNF suspensions are strongly shear thinning and display a yield stress, behaving as solids at rest and flowing readily under shear before rapidly recovering structure. This thixotropic behaviour is ideal for injectable depots and extrusion bioprinting (Bhattacharya et al., 2012). TOCNF gels can be strengthened by multivalent cations (Ca^{2+}, Zn^{2+}, Fe^{3+}), by acidification or by blending with cationic polymers, enabling in situ gelation. CNC suspensions, by contrast, are low in viscosity at moderate concentrations but form liquid crystalline phases and can be gelled by salt, by grafting thermo-responsive polymers or by combination with other polysaccharides.

3.2.3 Surface chemistry and modification

Each anhydroglucose unit carries three hydroxyl groups, though only those on the fibril surface are accessible. This surface is the platform for nearly every functionalisation strategy relevant to

drug delivery (Habibi, 2014). Modifications can be grouped into (i) adsorption of surfactants, polyelectrolytes or proteins; (ii) covalent small-molecule chemistry, including esterification, etherification, silylation, oxidation and amidation of carboxylated surfaces; and (iii) polymer grafting, either "grafting onto" preformed polymers or "grafting from" surface-initiated polymerisations such as atom transfer radical polymerisation (Eyley & Thielemans, 2014; Habibi, 2014). Hydrophobisation improves loading of poorly water-soluble drugs and compatibility with hydrophobic matrices, cationisation enhances interaction with anionic drugs and nucleic acids, and attachment of folic acid, peptides or antibodies supports active targeting.

Characterisation of surface chemistry is essential and often underreported. Conductometric titration quantifies charged groups, X-ray photoelectron spectroscopy and solid-state ^{13}C NMR verify substitution, and zeta potential describes colloidal behaviour. Degree of substitution, rather than reaction conditions alone, should be reported so that drug loading and biological outcomes can be compared across studies.

3.2.4 Optical, thermal and other properties

Individualised CNF films are highly transparent, an advantage for wound dressings that permit visual inspection and for ophthalmic and sensing applications. CNC chiral nematic films have been used as templates for photonic materials and colorimetric sensors. Thermal stability depends strongly on surface chemistry: sulfated and carboxylated nanocelluloses degrade at lower temperatures than unmodified ones, which matters for melt processing and for sterilisation by heat (Moon et al., 2011).

3.3 Biocompatibility, Immunological Response and Biodegradation

3.3.1 In vitro cytotoxicity

Most in vitro studies report low cytotoxicity of plant nanocellulose across fibroblasts, keratinocytes, macrophages, epithelial cells and stem cells at concentrations relevant to biomedical use (Jorfi & Foster, 2015; Roman, 2015). However, results vary considerably with particle type, dose, surface chemistry, aggregation state and assay. Cationic modifications and very high concentrations tend to raise toxicity, and some studies have observed oxidative stress or pro-inflammatory cytokine release in macrophages exposed to CNCs. Interference of nanocellulose with colorimetric assays (for example adsorption of dyes) and the confounding effect of endotoxin contamination have complicated interpretation (Nordli et al., 2016; Roman, 2015).

3.3.2 In vivo responses and inhalation concerns

Implantation studies of CNF scaffolds and hydrogels in rodents generally show mild foreign body responses comparable to those of established biomaterials, with fibrous encapsulation and limited inflammation. Subcutaneous injection of CNF hydrogels has been well tolerated in several reports. The principal safety concern relates to inhalation, by analogy with high-aspect-ratio fibres such as asbestos and carbon nanotubes. Pulmonary exposure studies in mice have

reported transient inflammatory responses to CNFs and CNCs, although these were generally milder than those to reference fibrous materials (Endes et al., 2016; Roman, 2015). A systematic review by Endes and colleagues concluded that the available data were insufficient for firm conclusions and that hazard depends strongly on material form, highlighting the need for standardised testing (Endes et al., 2016). Oral ingestion studies suggest low acute toxicity, consistent with the long history of cellulose in food, but chronic exposure data remain limited.

3.3.3 Biodegradation

Humans lack cellulases, so nanocellulose is not enzymatically degraded in most tissues; slow degradation may occur through oxidative and acid-catalysed processes or, in the gut, by microbial fermentation (Jorfi & Foster, 2015). For implants and injectable depots this persistence can be beneficial for long-term structural support but problematic when resorption is desired. Strategies to enhance degradability include periodate oxidation to dialdehyde cellulose, which renders chains susceptible to hydrolysis, co-delivery of cellulases within the construct, and reducing fibril size to aid clearance. Understanding the fate of nanocellulose fragments, including possible accumulation in organs of the reticuloendothelial system after systemic administration, remains a priority.

3.3.4 Occupational and environmental safety

Because the principal exposure route of concern is inhalation of dry powders and aerosols, safety assessment must extend beyond the patient to workers in production and formulation facilities. Occupational safety management systems that use near-miss and hazard observation data, proactive hazard recognition and data-driven risk control provide a framework for controlling exposure to airborne nanomaterials (Arumosoye & Obriki, 2019; Obogo et al., 2021a; Obriki & Arumosoye, 2018). Organisational learning, leadership-driven safety culture and institutionalised life-preserving practices are recognised determinants of sustained safety performance (Arumosoye & Obriki, 2021; Obogo et al., 2019a; Obriki & Arumosoye, 2019, 2021), while systematic hazard identification and incident prevention models support risk control in industrial environments (Obogo et al., 2019b, 2021b). Internal quality, health, safety and environment (QHSE) audits and critical reviews of safety management systems help verify compliance (Obogo et al., 2020a, 2020c), and governance of contractor safety is important where specialised maintenance is outsourced (Arumosoye & Obriki, 2020). Analyses of human error causation and of heat stress in industrial operations are equally applicable to facilities handling hot concentrated acids and oxidants (Arumosoye & Obriki, 2018; Obriki & Arumosoye, 2020).

Environmental frameworks developed for other contaminants also offer useful methods. Conceptual models that couple exposure biomarkers with individual susceptibility could be adapted to evaluate chronic nanocellulose exposure (Aladegba et al., 2021). Data-driven and spatially explicit models of subsurface contaminant migration can inform the management of acidic effluent and process residues from production sites (Azeez & Badmus, 2018; Lamidi & Olamide, 2018), and decision frameworks that reconcile chemical safety with circular-economy

goals for recycled polymers are relevant to the end-of-life handling of nanocellulose products (Okojie & Abioye, 2020).

3.4 Drug Delivery Potential

Plant nanocellulose can participate in drug delivery in several roles: as an excipient that modifies the release from conventional dosage forms, as a matrix (hydrogel, film or aerogel) in which a drug is dispersed, as a nanocarrier to which drugs are adsorbed or conjugated, and as a stabiliser of emulsions and nanoparticles. The dominant mechanisms controlling release are diffusion through the fibril network, electrostatic and hydrogen-bond interactions between drug and surface, and swelling or erosion of the matrix (Curvello et al., 2019; Lin & Dufresne, 2014; Plackett et al., 2014).

3.4.1 Oral solid dosage forms and excipients

Microcrystalline cellulose is already one of the most widely used tablet excipients, and nanocellulose is a natural successor. CNF powders and films have been used to produce matrix systems that sustain the release of model drugs over periods of up to several months, owing to the dense, tortuous network formed on drying. Kolakovic and colleagues showed that spray-dried CNF microparticles could sustain the release of poorly soluble model drugs and that CNF films could act as long-term release matrices (Kolakovic et al., 2012). CNF has also been used as a binder and disintegrant modifier and to stabilise amorphous drug forms. CNCs adsorb ionisable water-soluble drugs such as tetracycline and doxorubicin hydrochloride in large amounts through electrostatic interaction with sulfate groups, and cationic surfactant modification of CNCs enables binding of hydrophobic anticancer agents such as docetaxel, paclitaxel and etoposide (Jackson et al., 2011; Plackett et al., 2014).

Sustained-release oral systems are particularly relevant to chronic non-communicable diseases that require long-term pharmacotherapy and in which non-adherence is common. Reduced dosing frequency enabled by nanocellulose matrices could complement mobile health solutions for chronic disease monitoring and treatment adherence (Oparah et al., 2021b).

3.4.2 Injectable and in situ forming hydrogels

The shear-thinning, rapidly recovering nature of CNF gels permits injection through fine needles followed by in situ reformation of a depot. Commercial wood-derived CNF hydrogels have been shown to support three-dimensional culture of hepatocyte cell lines and to provide sustained release of small molecules and proteins, including model antibodies, with release rates governed by molecular size and network density (Bhattacharya et al., 2012; Paukkonen et al., 2017). Ion-crosslinked TOCNF gels allow tuning of stiffness and release via the choice and concentration of cation. Composite gels combining CNCs with thermo-responsive polymers such as poly(N-isopropylacrylamide) or Pluronic copolymers, or with chitosan, alginate and hyaluronic acid, produce formulations that are fluid at room temperature and gel at body temperature (Du et al., 2019; Eyley & Thielemans, 2014). Dynamic covalent crosslinking, for example Schiff base

bonds between dialdehyde cellulose nanocrystals and amine-bearing polymers, provides self-healing injectable gels with controlled degradation.

3.4.3 Nanocarriers for targeted and stimuli-responsive delivery

The small size and functional surface of CNCs make them candidate nanocarriers for systemic and cellular delivery. Folic-acid-conjugated CNCs showed receptor-mediated uptake by folate-receptor-positive cancer cells, demonstrating feasibility of active targeting (Dong et al., 2014). CNCs bearing cyclodextrin moieties form inclusion complexes with hydrophobic drugs, and polymer-grafted CNCs have been designed to respond to pH, temperature, redox potential and enzymes. pH-responsive systems exploit the acidic environments of tumours, endosomes and inflamed tissue, for example through acid-labile hydrazone linkages or pH-dependent swelling of grafted polyelectrolytes. Hybrid carriers in which nanocellulose supports metal or metal oxide nanoparticles (silver, gold, iron oxide, zinc oxide) add antimicrobial, photothermal or magnetic functionality (Seabra et al., 2018). Cationic nanocellulose derivatives complex plasmid DNA and siRNA, although transfection efficiencies have generally been lower than those of established vectors.

Despite these encouraging results, the systemic delivery of rod-like CNCs raises unresolved questions about biodistribution, circulation time, protein corona formation and clearance. To date, most targeted carrier studies are limited to cell culture, and relatively few report pharmacokinetics or efficacy in animal models. This gap represents a key opportunity and challenge for the field.

Targeted carriers will ultimately be judged against clinical diagnostic endpoints. Barriers to the adoption of immunohistochemistry in oncology diagnostics, and the need for strengthened diagnostic quality systems in resource-limited laboratories, illustrate the analytical capacity required to evaluate targeted nanocellulose systems in patients (Abdulrazaq et al., 2021; Yusuf & Abdulrazaq, 2018).

3.4.4 Transdermal, topical and wound-healing systems

Nanocellulose films, membranes and hydrogels are well suited to topical and transdermal delivery because they conform to skin, maintain a moist wound environment, absorb exudate and can be transparent. Plant CNF dressings loaded with antibiotics (for example tetracycline or ciprofloxacin), silver nanoparticles, antimicrobial peptides or plant extracts have shown sustained antimicrobial activity in vitro and accelerated healing in animal wound models (Lin & Dufresne, 2014; Liu et al., 2018). Clinical experience with bacterial cellulose dressings, already marketed for burns and chronic wounds, provides a useful reference point, and early clinical studies with wood-derived CNF dressings in skin graft donor sites have reported performance comparable to commercial products. Microneedle patches incorporating nanocellulose and transdermal patches using CNC-reinforced matrices are further emerging formats.

Antimicrobial nanocellulose dressings must be positioned within wider infection management practice. Traditionally used botanicals with documented in vitro antimicrobial activity are candidate natural payloads for such dressings (Gbadamosi & Obogo, 2013). Integrated laboratory information systems that improve infection detection, and multi-laboratory networks for antimicrobial resistance surveillance, are needed to match therapy to pathogens and to monitor resistance as new antimicrobial dressings are introduced (Abdulrazaq et al., 2019; Yusuf et al., 2020).

3.4.5 Aerogels, foams and Pickering emulsions

Freeze-dried and supercritically dried nanocellulose aerogels have porosities above 95% and specific surface areas that can exceed 200 $m^2\ g^{-1}$, offering high loading capacity and floating behaviour for gastro-retentive delivery. Release from aerogels can be tuned by crosslinking, surface hydrophobisation and coating (De France et al., 2017). CNCs and CNFs are also effective Pickering stabilisers of oil-in-water emulsions without synthetic surfactants, enabling encapsulation of lipophilic drugs, vitamins and essential oils for oral, topical or injectable use.

3.4.6 Mucosal, ocular and other routes

Mucoadhesive properties of nanocellulose, enhanced by blending with chitosan or by thiolation, have been exploited in buccal, nasal and vaginal formulations. Transparent CNF films and gels have been evaluated for ocular inserts and contact-lens-related release. Nanocellulose has also been incorporated into implant coatings for local antibiotic release and into scaffolds that deliver growth factors or osteogenic agents.

Table 3. Representative drug delivery strategies using plant-derived nanocellulose.

Platform	**Nanocellulose type and modification**	**Example payloads**	**Release control / key feature**
Oral matrix tablets, films, microparticles	CNF (unmodified or TOCNF)	Poorly soluble model drugs, itraconazole, indomethacin	Dense network; sustained release over days to months
Ionic drug binding	Sulfated CNC; TOCNF; cationic CNF	Tetracycline, doxorubicin HCl, anionic NSAIDs	Electrostatic binding; pH and ionic strength dependent
Hydrophobic drug carriers	CNC with cationic surfactant, cyclodextrin or polymer grafts	Paclitaxel, docetaxel, curcumin	Hydrophobic domains; inclusion complexes

Platform	Nanocellulose type and modification	Example payloads	Release control / key feature
Injectable hydrogels	CNF; TOCNF crosslinked with Ca^{2+}; CNC/thermo-responsive polymer composites	Proteins, antibodies, small molecules	Shear-thinning depot; size-dependent diffusion
Targeted nanocarriers	Carboxylated or aminated CNC with folate or peptide ligands	Anticancer agents, imaging probes	Receptor-mediated uptake; pH/redox triggers
Wound dressings, transdermal systems	CNF films, aerogels, composite gels with Ag NPs	Antibiotics, silver, antimicrobial peptides, extracts	Moist environment, exudate uptake, sustained antimicrobial action
Aerogels and Pickering emulsions	CNF/CNC aerogels; CNC-stabilised emulsions	Lipophilic drugs, vitamins, essential oils	High loading, gastro-retention, surfactant-free encapsulation

3.5 Intersections with Tissue Engineering and 3D Bioprinting

Many drug delivery advances with nanocellulose arise within tissue engineering, where scaffolds both support cells and release bioactive cues. Nanocellulose is an attractive component of bioinks because CNF provides shear thinning and shape fidelity while a second component, typically alginate, gelatin methacryloyl or hyaluronic acid, offers crosslinking and cell-adhesive ligands. Markstedt and colleagues demonstrated a CNF/alginate bioink for printing human chondrocyte-laden constructs with high resolution and good cell viability, a result that has been widely extended (Markstedt et al., 2015). Nanocellulose-based scaffolds have been investigated for cartilage, bone (often combined with hydroxyapatite or bioactive glass), skin, nerve guidance conduits, cardiac patches and three-dimensional tumour and liver models for drug screening. Because nanocellulose lacks intrinsic cell-binding motifs, adhesion is commonly promoted by protein adsorption, RGD peptide conjugation or blending with collagen and gelatin. Scaffolds that deliver growth factors, antibiotics or anti-inflammatory drugs in a controlled manner represent a convergence of the delivery and regenerative functions discussed here.

3.6 Conceptual Model

3.6.1 Development of the model

The thematic synthesis revealed a consistent pattern: decisions made at the processing stage propagate through material structure and function to delivery performance, and the step from

laboratory performance to patient benefit depends on conditions that lie largely outside materials science. These observations were integrated into a Process-Structure-Function-Translation (PSFT) model (Figure 1), developed by identifying the concepts recurring in the literature, mapping their relationships and testing the coherence of the resulting framework against the evidence (Jabareen, 2009). The model extends the process-structure-property paradigm of materials science to include delivery performance and translational outcomes, and it adds an enabling layer and a feedback loop.

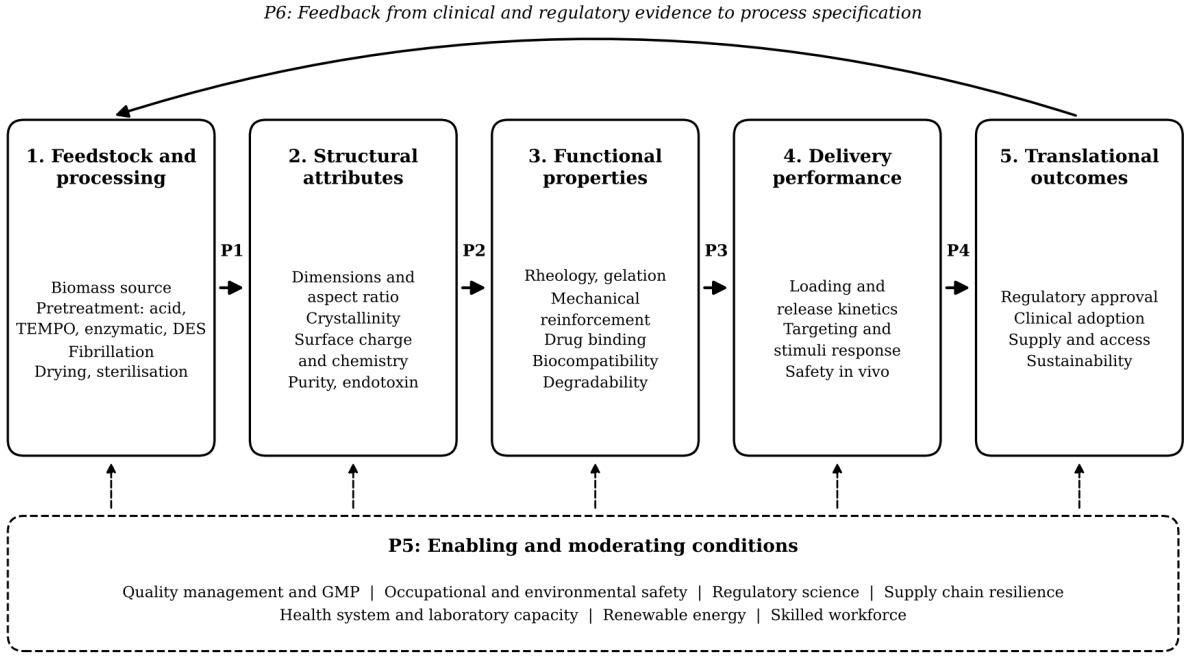


Figure 1. The Process-Structure-Function-Translation (PSFT) conceptual model for plant-derived nanocellulose in drug delivery. Solid arrows denote the main causal chain (P1 to P4); the dashed layer denotes enabling and moderating conditions (P5); the curved arrow denotes feedback from clinical and regulatory evidence to process specification (P6).

3.6.2 Model constructs

Stage 1, feedstock and processing, comprises the biomass source, purification, the hydrolysis, oxidation or enzymatic pretreatment, mechanical fibrillation, surface modification, drying and sterilisation (Section 3.1). Stage 2, structural attributes, comprises the dimensions and aspect ratio, crystallinity, surface charge and chemistry, degree of substitution, and purity including endotoxin content (Sections 3.1 and 3.2). Stage 3, functional properties, comprises rheology and gelation, mechanical reinforcement, drug binding capacity, biocompatibility and degradability (Sections 3.2 and 3.3). Stage 4, delivery performance, comprises drug loading, release kinetics, targeting, responsiveness to stimuli and in vivo safety (Section 3.4). Stage 5, translational outcomes, comprises regulatory approval, clinical adoption, supply and access, and sustainability.

The enabling layer contains the conditions identified in the translational stream: quality management and GMP, occupational and environmental safety, regulatory science, supply chain resilience, health system and laboratory capacity, renewable energy and a skilled workforce. These conditions do not create material functionality, but they determine whether functionality can be produced reproducibly, safely and at scale, and whether the resulting products reach patients.

3.6.3 Propositions

The model is expressed as six propositions, summarised with their supporting evidence in Table 4.

Table 4. Propositions of the PSFT model and supporting evidence.

No.	Statement	Principal supporting evidence
P1	Feedstock and processing route determine the structural attributes of nanocellulose.	Acid hydrolysis yields sulfated rod-like CNCs, while TEMPO oxidation yields individualised carboxylated fibrils (Habibi et al., 2010; Isogai et al., 2011; Moon et al., 2011; Saito et al., 2007); feedstock affects crystallinity and residual components (Trache et al., 2017).
P2	Structural attributes govern functional properties relevant to biomedicine.	Aspect ratio and charge govern gelation and rheology (Bhattacharya et al., 2012; De France et al., 2017); surface chemistry governs reactivity and binding (Eyley & Thielemans, 2014; Habibi, 2014); purity and endotoxin influence apparent biocompatibility (Endes et al., 2016; Nordli et al., 2016).
P3	Functional properties determine delivery performance.	Network density and ionic interactions control release from films, gels and particles (Jackson et al., 2011; Kolakovic et al., 2012; Paukkonen et al., 2017); ligand conjugation enables targeting (Dong et al., 2014).
P4	Delivery performance leads to translational outcomes only when safety, biodistribution and degradation evidence is available.	Toxicological and in vivo evidence remains incomplete (Endes et al., 2016; Roman, 2015; Seabra et al., 2018).

No.	Statement	Principal supporting evidence
P5	Enabling conditions moderate every transition in the chain.	GMP and quality systems (Aneke & Adesemoye, 2020; Obukadata et al., 2021a); occupational safety (Arumosoye & Obriki, 2019; Obogo et al., 2021a); traceability and regulatory compliance (Aneke & Adesemoye, 2019, 2021); supply chain resilience (Anene, 2021; Nnabueze et al., 2021); health system capacity (Ilodigwe & Adesemoye, 2019b, 2020); workforce (Orise & Niniola, 2020).
P6	Clinical and regulatory evidence should feed back to define target product profiles and critical material attributes at the processing stage.	Risk-based quality management in GMP environments (Aneke & Adesemoye, 2020); need for standardised characterisation (Endes et al., 2016; Jorfi & Foster, 2015).

Proposition P1 states that processing determines structure. The evidence is strongest here: the chemistry of each isolation route predictably sets particle morphology and surface groups (Habibi et al., 2010; Isogai et al., 2011; Saito et al., 2007). Proposition P2 states that structure governs function, which is well supported for rheology and surface reactivity but less consistently for biocompatibility, where outcomes are confounded by impurities and assay interference (Nordli et al., 2016; Roman, 2015). Proposition P3 links function to delivery performance and is supported by release studies, although most use model drugs (Kolakovic et al., 2012; Paukkonen et al., 2017). Proposition P4 identifies the evidence gap that currently limits translation. Proposition P5 recognises that enabling conditions moderate every stage, and Proposition P6 calls for a quality-by-design logic in which clinical requirements specify upstream material attributes.

3.7 Discussion of Principal Findings

With respect to RQ1, the literature shows that processing is the dominant determinant of nanocellulose properties. Sulfuric acid hydrolysis, TEMPO-mediated oxidation, enzymatic pretreatment and purely mechanical fibrillation produce materials that differ by an order of magnitude in width and length, by several-fold in surface charge, and in purity and thermal stability (Isogai et al., 2011; Moon et al., 2011; Siró & Plackett, 2010). Because these attributes control gelation, drug binding and cell responses, the descriptor "nanocellulose" alone is insufficient to predict biological behaviour, and many apparent contradictions in the literature reflect undocumented differences in material (Endes et al., 2016; Jorfi & Foster, 2015).

With respect to RQ2, the evidence indicates a gradient of maturity. Oral sustained-release matrices and topical wound dressings are the most advanced applications, supported by the long

record of cellulose excipients and by early clinical experience with cellulose dressings (Kolakovic et al., 2012; Lin & Dufresne, 2014). Injectable and in situ forming hydrogels show strong preclinical promise because of their shear-thinning behaviour and tunable release (Bhattacharya et al., 2012; Du et al., 2019; Paukkonen et al., 2017). Targeted systemic nanocarriers, despite attractive in vitro results, remain at an early stage because pharmacokinetic, biodistribution and clearance data are scarce (Dong et al., 2014; Seabra et al., 2018).

With respect to RQ3, the translational literature indicates that the binding constraints are increasingly outside the laboratory. Reproducible biomedical-grade production requires quality systems and process equipment designed for corrosive and high-pressure operations (Aneke & Adesemoye, 2020; Obetta et al., 2020, 2021); worker safety must address inhalation of fine powders (Arumosoye & Obriki, 2019; Obogo et al., 2021a); and regulatory traceability, supply chain resilience and health system capacity determine whether new products reach patients (Aneke & Adesemoye, 2019; Anene, 2021; Ilodigwe & Adesemoye, 2019b). In sub-Saharan Africa, abundant residues such as cassava peels create an opportunity for regional production (Aye & Tawose, 2015, 2016), but realising it depends on these enabling conditions.

3.8 Barriers to Clinical Translation

Integrating these findings, seven barriers stand out.

- Standardisation and reproducibility. Nanocellulose properties vary with feedstock, season, pulping history and processing. Biomedical grades require tightly specified dimensions, surface chemistry, purity, endotoxin levels and microbial limits, ideally produced under good manufacturing practice. Harmonised terminology and measurement standards, such as those developed through ISO and TAPPI committees, should be adopted consistently in the research literature.
- Comprehensive safety assessment. Long-term, route-specific toxicology, genotoxicity and immunotoxicity data remain sparse, and many studies use poorly characterised materials. Reporting particle dimensions, aggregation state in the test medium, surface chemistry and endotoxin content should become standard.
- Pharmacokinetics and biodistribution. Systemic nanocarrier claims require in vivo tracking of nanocellulose itself, not only of the payload, together with clearance and organ accumulation data.
- Controlled degradation. Designing nanocellulose systems that resorb on a predictable timescale, through oxidation, co-delivered enzymes or composite design, would broaden the range of implantable and injectable applications.
- Release performance. Burst release of small, water-soluble drugs from porous networks is common. Strategies such as covalent conjugation with cleavable linkers, multilayer coatings and hybrid inorganic-organic systems are needed to achieve zero-order or triggered release.

- Regulatory pathways. Unmodified cellulose benefits from a favourable regulatory history, but chemically modified nanocelluloses are likely to be regarded as new materials. Early dialogue with regulators and the use of established pharmacopoeial frameworks will be important.
- Sustainability and local value chains. Life cycle assessments should accompany process development so that greener routes are verified rather than assumed. Use of agricultural residues offers economic opportunities for countries with large biomass resources but limited pharmaceutical manufacturing capacity.

3.9 Contribution Relative to Previous Reviews

Earlier reviews have described nanocellulose production, properties and biomedical potential comprehensively (Jorfi & Foster, 2015; Klemm et al., 2011; Lin & Dufresne, 2014; Moon et al., 2011), and others have examined drug delivery (Plackett et al., 2014; Seabra et al., 2018) or hydrogels (De France et al., 2017; Du et al., 2019) in depth. The present review contributes in two ways. It links processing choices explicitly to delivery performance through a single causal chain, and it integrates the translational conditions that previous reviews have mentioned only briefly into a conceptual model with testable propositions. In doing so, it brings the perspective of emerging economies, where feedstock availability and manufacturing constraints differ from those in established producer countries, into the discussion of nanocellulose biomedicine.

3.10 Implications

3.10.1 Theoretical implications

The PSFT model extends the process-structure-property paradigm of materials science into translational science. By treating delivery performance and translational outcomes as explicit stages, and by specifying enabling conditions as moderators, it offers a framework in which materials, pharmaceutical and health systems research can be connected. Each proposition can be tested empirically, for example by design-of-experiments studies that relate processing variables to structural and functional responses (P1 to P3), or by comparative case studies of product development programmes (P5 and P6).

3.10.2 Practical implications for researchers and manufacturers

For researchers, the model implies that every biomedical study should report the critical material attributes that link processing to performance: dimensions, crystallinity, surface chemistry and degree of substitution, charge, and endotoxin and microbial levels (Endes et al., 2016; Jorfi & Foster, 2015; Nordli et al., 2016). For formulation design, it suggests matching material to application: TEMPO-oxidised CNFs for ion-crosslinkable gels and cationic drug binding, cationic CNFs for anionic drugs and nucleic acids, sulfated or carboxylated CNCs for nanocarriers, and unmodified or enzymatic CNFs where minimal chemical modification is preferred (Habibi, 2014; Isogai et al., 2011; Jackson et al., 2011; Saito et al., 2007). For manufacturers, the model points to quality-by-design, Lean Six Sigma and GMP-aligned quality

systems as prerequisites for biomedical grades (Ambali et al., 2021; Aneke & Adesemoye, 2020; Obukadata et al., 2021a).

3.10.3 Regulatory science and medicine quality

Regulatory translation will depend on broader developments in medicine quality assurance. Traceability and chain-of-custody integrity in pharmaceutical distribution, risk-based import compliance and the interdiction of illicit medical products define expectations that new nanocellulose-based products will face (Aneke & Adesemoye, 2019, 2021). Risk-based decision-making in GMP environments and digitally enabled manufacturing provide the quality framework for producing pharmaceutical-grade nanocellulose (Aneke & Adesemoye, 2020; Obukadata et al., 2021a), and Lean Six Sigma has been applied to remove distribution bottlenecks for medicines in developing healthcare settings (Obukadata et al., 2021b). Tamper-proof regulatory recordkeeping, data protection governance and ISO-aligned digital supply chain controls support the auditable records that regulators require (Anichukwueze et al., 2021; Mbonu et al., 2018, 2019, 2020).

3.10.4 Supply chains and procurement

Supply chain considerations are equally important. End-to-end visibility and traceability frameworks, supplier relationship management, and resilience and risk management strategies developed after recent global disruptions are relevant to securing consistent supplies of biomedical-grade nanocellulose (Anene, 2021; Ike et al., 2021; Nnabueze et al., 2021; Ogunwole et al., 2021). ESG-integrated sustainable procurement models support responsible sourcing of biomass and chemicals (Okojie et al., 2020), and shared responsibility across jurisdictions is important where feedstocks, processing and formulation occur in different countries (Ominyi et al., 2021). Predictive demand forecasting, procurement automation, real-time order visibility, materials readiness planning and vendor governance can reduce inventory costs and lead times (Aifuwa et al., 2020; Akinleye & Adeyoyin, 2021; Ebisi et al., 2021; Okonkwo et al., 2019, 2021), while legal barriers to import and export participation affect entrepreneurs seeking to trade nanocellulose products from West Africa (Jones & Ominyi, 2020).

3.10.5 Health system readiness and clinical infrastructure

Scientific advances in materials will not improve patient outcomes without the health system capacity to deliver them, as conceptual analyses of the gap between molecular innovation and patient outcomes have emphasised (Ilodigwe & Adesemoye, 2019b). Pharmacy-led delivery models, interoperable health data infrastructure and sustainable health financing mechanisms determine whether new formulations become accessible (Ilodigwe & Adesemoye, 2019a, 2020, 2021), and the financing and procurement of capital equipment shape the adoption of new healthcare technologies (Okoli et al., 2020). Clinical evaluation of nanocellulose products will also require appropriate laboratory and diagnostic infrastructure, including sustainable diagnostic laboratory models, expanded diagnostic access in underserved regions, regulatory-compliant molecular and pathology laboratories and well-planned laboratory spaces (Aminu-Ibrahim et al.,

2018, 2020; Ogbete et al., 2018, 2019). Sustainable materials selection and energy efficiency in laboratory facilities (Ogbete et al., 2020), and risk-managed construction and coordinated multi-site programme management for regulated healthcare facilities, are further enabling elements (Aminu-Ibrahim et al., 2019, 2021; Ogbete et al., 2021). Disease surveillance systems with reliable data quality and AI-based risk stratification would support post-market monitoring of new therapies (Ekemezie et al., 2018; Oparah et al., 2021a).

3.10.6 Workforce and capacity building

Building the scientific and technical workforce is critical. Data-informed digital learning platforms for healthcare and STEM, offline-first designs for low-connectivity environments and industry-academia collaboration for technical learning centres can help prepare the multidisciplinary specialists that nanocellulose biomedicine requires (Nwangwu et al., 2019; Orise & Niniola, 2020; Unamma et al., 2018). Talent development across distributed operations, strategic recruitment in emerging-market enterprises and standardised change management mechanisms will support the organisations that commercialise these materials (Akhigbe et al., 2020; Falemi et al., 2020; Uzondu et al., 2021).

4. Conclusion

Plant-derived cellulose nanomaterials combine renewable origin, mechanical robustness, rich surface chemistry and generally favourable biocompatibility, making them versatile platforms for biomedical engineering. Processing choices, from feedstock and pretreatment to fibrillation, modification, drying and sterilisation, decisively shape particle morphology, charge, purity and therefore biological performance. In drug delivery, nanocellulose has shown value as a sustained-release excipient, an injectable and shear-thinning depot, a functionalisable nanocarrier, a wound-healing matrix and a stabiliser of emulsions and aerogels. The most mature applications are in oral formulations and topical wound care, whereas systemic targeted delivery remains at an early, largely preclinical stage. Addressing material standardisation, long-term safety, in vivo fate and regulatory clarity will determine how quickly these materials progress from promising laboratory systems to clinical products.

By integrating these findings into the Process-Structure-Function-Translation model, this review provides a framework that links processing decisions to clinical outcomes and highlights the enabling conditions that must be in place for translation. Testing its propositions, standardising material characterisation and generating long-term in vivo evidence are the most important next steps for the field.

4.1 Limitations

This review has several limitations. First, it uses an integrative rather than a fully systematic design, and no protocol was registered; although the search was structured, selection and appraisal involved judgement and may be subject to bias. Second, only English-language, peer-reviewed sources published between 2005 and 2021 were included, so relevant work in other

languages, in patents and in industrial grey literature, and developments after 2021, are not represented. Third, the heterogeneity of materials, models and outcome measures precluded meta-analysis, and quantitative statements are therefore indicative ranges rather than pooled estimates. Fourth, much of the translational stream consists of conceptual frameworks from adjacent fields such as pharmaceutical operations, occupational safety and supply chain management; their application to nanocellulose is by analogy and requires confirmation. Finally, the PSFT model is derived from the literature and has not yet been validated empirically.

4.2 Future Research

The synthesis and the PSFT model suggest the following research agenda:

- Standardised characterisation and reporting. Consensus minimum reporting standards for biomedical nanocellulose, covering dimensions, surface chemistry, crystallinity, endotoxin and sterilisation method, are needed to make studies comparable and to test propositions P1 and P2.
- Long-term safety, biodistribution and degradation. Studies using labelled nanocellulose should track the material itself after oral, topical, injectable and inhalation exposure, and should establish degradation kinetics for oxidised and enzyme-responsive variants (proposition P4).
- Empirical validation of the model. Design-of-experiments and multivariate modelling studies should quantify the relationships between processing variables, structural attributes and release performance, and machine-learning approaches could predict functional outcomes from processing data.
- Residue-based biomedical-grade production. Research should evaluate cassava peels and other regional residues as feedstocks for biomedical-grade nanocellulose, combined with techno-economic analysis and life cycle assessment that includes renewable energy options.
- Clinical evaluation. Well-designed clinical trials of nanocellulose wound dressings and oral sustained-release formulations are needed to establish efficacy and safety in patients.
- Regulatory and translational science. Studies should clarify how chemically modified nanocelluloses are classified, which non-clinical data regulators require, and how enabling conditions (proposition P5) affect development timelines, particularly in emerging economies.

Promising directions include the integration of nanocellulose with smart and sensing functions, for example dressings that report infection through colour changes; personalised dosage forms produced by three-dimensional printing; combination with mRNA and protein therapeutics; and the use of machine-learning approaches to relate processing parameters to functional outcomes. Close collaboration between materials scientists, pharmaceutical scientists, toxicologists and clinicians will be essential to translate the material's considerable promise into therapeutic benefit.

Conflict of Interest

The authors declare no conflict of interest.

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