RSC Applied Interfaces

REVIEW

View Article Online
View Journal

Cite this: DOI: 10.1039/d5lf00377f

Lignin-based biopharmaceuticals from nature to medicine: current trends, future prospects and emerging challenges

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Lignin, a renewable and widespread aromatic biopolymer constituting 15–40% of the dry weight of lignocellulosic biomass, is a principal component of plant cell walls. Its inherent properties, including biocompatibility, antioxidant potential, antimicrobial activity, UV absorption, and higher mechanical strength, make it a highly promising sustainable material. This review comprehensively describes the potential of lignin for biopharmaceutical products by corroborating its fundamental properties, sources, and biomedical applications. A major focus is on the critical translational challenges, including detailed discussions of physicochemical properties, toxicological implications, safety assessment, and regulatory hurdles. Lignin-based biopharmaceuticals hold great promise for sustainable healthcare, but their safe and successful commercialization requires more comprehensive research and the establishment of clear regulatory frameworks to ensure the safe commercialization and sustainable development of lignin-based healthcare solutions urgently.

Received 1st December 2025,
Accepted 15th February 2026

DOI: 10.1039/d5lf00377f

rsc.li/RSCApplInter

1. Introduction

1.1 Overview of lignin

Lignin is a highly complex polyphenolic biopolymer that has gained interest as a sustainable material for diverse industrial and biopharmaceutical applications due to its diversity in structure and potential utilization. It is the second most abundant natural polymer and a principal component of lignocellulosic biomass.[1–3] More than 50 million tons of lignin-based materials and chemicals are produced every year globally, showing the abundance of lignin and its potential for large-scale utilization.[4]

1.2 Extraction and types of lignin

The extraction and solubilization of lignin are challenging due to its structural complexity and poor solubility in most conventional solvents.[5] Lignin's solubility depends on the method used in the delignification of biomass.[5] In the Kraft process, Kraft lignin (KL) is extracted from biomass using an aqueous solution containing sodium hydroxide and sodium sulfide, yielding a lignin product with a relatively low ash content. Additionally, KL is soluble in alkali solutions and various polar organic solvents due to its sulfur content. In KL, G-type units are dominantly present, as well as its high phenolic content, which may indicate that it would contain many reactive potential active sites for further functionalization, cross-linking, or polymerization.[6] On the other hand, for the extraction of alkali lignin, the soda process utilizes alkaline agents such as sodium hydroxide, potassium hydroxide, or calcium hydroxide to hydrolytically break the linkage between lignin and carbohydrates. The surface functionality of alkali lignin is dominated by phenolic hydroxyl (–OH), aliphatic hydroxyl, and methoxyl ($-OCH_3$) groups, which are crucial for its surface-active and antioxidative properties. The organosolv process, which employs organic solvents under milder conditions, yields lignin of higher purity with lower sulfur content, and makes more suitable for biomedical uses. Organosolv lignin with a higher S-type unit content exhibits better reducing power, resulting in greater antioxidant properties.[7] Modern techniques such as solvent extraction, membrane ultrafiltration, and enzymatic fractionation are increasingly employed to obtain native-like lignin with improved structural homogeneity and biocompatibility.[8] These approaches are particularly valuable because industrial or technical lignin,

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although abundant, often contains sulfur and metal impurities that limit reproducibility and make it unsuitable for direct biomedical use without further purification.[9,10]

1.3 Structural characteristics and monomeric units

Structurally, lignin is an amorphous, highly branched polymer composed of phenolic monomers, predominantly *p*-coumaryl alcohol, coniferyl alcohol, and sinapyl alcohol. These monomers polymerize into *p*-hydroxyphenyl, guaiacol, and syringyl units (Fig. 1). Lignin's molecular complexity arises from different chemical bonds that connect its monomers, such as β-O-4, 5-5, β-5, β-1, 4-O-5, and β-β linkages.[11] The relative abundance of H, G, and S monomers varies depending on the plant source. The variation in the lignin monomer ratio leads to different functional group densities.[12] Different types of lignin and their monomer unit ratios are accountable for the variations in their activity, such as antioxidant and antimicrobial (Table 1). Softwoods are typically rich in guaiacyl units, while hardwoods contain both guaiacyl and syringyl units.[13] For example, Sun *et al.* observed that very high total phenolic –OH (3.28 mmol g^{-1}) and –COOH (3.03 mmol g^{-1}) contents lead to superior reducing ability, nucleation density, and metal coordination, resulting in well-dispersed, uniform nanoparticles. Low or fewer accessible phenolic/carboxyl sites and greater steric hindrance produce less uniform nanoparticles.[13] These observations suggest that variation in monomer composition plays a significant role in determining functional group density and application.

Analytical characterization plays a key role in elucidating this complexity. Techniques such as gel permeation chromatography (GPC), ^{31}P NMR, and FT-IR spectroscopy have been utilized to characterize the variety of lignin. They provide insight into the complex and heterogeneous structure

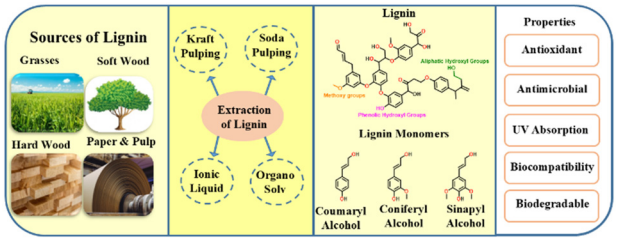

Fig. 1 Schematic overview of sources, extraction methods, the lignin structure, and its properties.

of lignin, including its molecular weight, functional groups, and chemical structure. Other techniques, such as UV-vis spectroscopy, SEM/TEM, and XPS, can be used in assessing conjugation and chromophore content, morphological evaluation, and surface chemical analysis. Together, these techniques provide critical insight into lignin's heterogeneity and enable correlations between the molecular structure and biomedical performance.[13]

1.4 Physicochemical and biological properties relevant to biopharmaceutical use

Lignin's structural intricacy imparts a range of physicochemical and biological functionalities critical for biomedical applications. Its aromatic rings and phenolic hydroxyl and methoxy groups contribute to strong antioxidant and antimicrobial properties. Additionally, the phenolic groups found in lignin may interfere with the bacterial cell membrane, resulting in cell lysis and enhancing the antimicrobial activity.[14]

Lignin has practical application as a substitute for traditional and chemical ingredients in numerous pharmaceuticals based on UV-blocking properties.[15–17]

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Table 1 Summary of different lignin types, dominant units, and their relative activities

Types of lignin	Solubility	M. wt (Da)	Zeta potential (mV)	H/G/S ratio	Dominant unit	Antioxidant activity	Antimicrobial activity
Kraft lignin	Alkali, organic solvents	3700–19 800	−40 to −45	5 : 90 : 5 (softwood KL) 5 : 50 : 45 (hardwood KL)	Guaiacyl	Moderate	Moderate to high
Lignosulfonate	Water	12 000–60 000	−25 to −30	5 : 90 : 5 (softwood) 5 : 50 : 45 (hardwood) 20 : 50 : 30 (grass-based)	—	High	Moderate
Soda lignin	Alkali	1300–1400	−20 to −40	20 : 50 : 30 (highly variable depending on the source)	Mixed (H/G)	Very high	High
Organosolv	Organic solvents	4100–10 800	−8 to −12	5 : 90 : 5 (softwood) 5 : 40 : 55 (hardwood organosolv)	Syringyl	High	Moderate

Besides biomedical uses, the antioxidant properties of lignin make it a promising additive in food and cosmetic products, where it can prevent oxidative reactions, slow down ageing processes, and enhance product stability.[15,16,18]

The antioxidant activity of lignin arises from the presence of phenolic hydroxyl (–OH) groups in its structure. These phenolic moieties act as hydrogen atom donors, neutralizing reactive oxygen species (ROS) and free radicals by converting them into more stable, non-reactive molecules. In this process, a phenoxy radical is formed, which is stabilized through resonance across the aromatic lignin backbone, thus preventing further radical propagation. Additionally, the conjugated π-electron system of lignin facilitates electron delocalization, enhancing its radical scavenging efficiency.[19,20]

The antibacterial activity of lignin is due to the interaction of lignin with microbial cellular structure. The hydrophobic aromatic groups of lignin associate with phospholipid bilayers in bacterial membranes, increasing membrane permeability and causing leakage of intracellular components. Additionally, low-molecular-weight phenolic groups released during lignin degradation can interfere with microbial metabolic enzymes, impair ATP synthesis, and induce oxidative stress within the cell. Consequently, these effects compromise membrane integrity, inhibit cellular respiration, and ultimately lead to pathogen growth inhibition.[21,22] All these features make lignin a potential candidate for numerous biomedical applications, such as anti-aging treatments, wound healing, and tissue engineering.

1.5 Suitability for biomedical use and purification needs

Lignin's polyphenolic structure and abundance of functional groups, including hydroxyl, methoxy, and carboxyl moieties, make it an attractive biopolymer for biomedical materials and applications, particularly due to its antioxidant activity and chemical versatility. However, not all types of lignin are suitable for biomedical or biopharmaceutical use in their native form. Technical lignin such as alkali lignin, KL, soda lignin, and LS often contains sulfur residues, metal ions, and other process-related impurities, which contribute to chemical heterogeneity and limited reproducibility.[10]

Recent studies focused on different types of lignin, such as those extracted using organosolv, enzymatic hydrolysis, and mild extraction or fractionation processes, which demonstrated structural homogeneity, low impurity, and high biocompatibility. In addition to their properties, high antioxidant potential makes them suitable for biomedical applications.[23,24] Organosolv lignin is more suitable for biomedical applications due to its relatively low molecular weight and high content of phenolic hydroxyl groups, which enhance antioxidant activity through efficient radical scavenging. Its low sulfur content and high chemical purity improve hydrophobicity, interfacial packing, and colloidal stability during nanoparticle or emulsion formulation. In contrast, other types of technical lignin typically exhibit higher molecular weight, greater polydispersity, and higher impurity levels, leading to reduced antioxidant efficiency and poorer formulation stability.[25] Techniques like solvent extraction, membrane ultrafiltration, or enzymatic treatment can be utilized to attain extra purity, maintaining the quality and biocompatibility of lignin.[8]

Despite encouraging laboratory findings, most lignin-based biomedical applications continue at the laboratory or proof-of-concept stage. The industrial scalability and regulatory amenability of lignin-derived biomaterials still need to be authenticated. Thus, recognizing and optimizing lignin extraction and purification approaches remain a critical upstream research challenge for understanding the biomedical potential of lignin and improving the overall economic viability of lignin valorization.

This review comprises recent studies on emergent interest in lignin-based biopharmaceutical as sustainable alternatives to conventional pharmaceuticals. By linking lignin's chemical versatility and biological functionality with formulation design, this review aims to provide a framework for the rational development of lignin-derived materials in pharmaceutical sciences. This review offers insights to provide a new path for potential applications of different lignin-based formulations (solid, semi-solid, and liquid) in various biotherapeutic applications, such as drug delivery and tissue regeneration. As lignin has unique properties such as UV absorption capacity, minimal cytotoxicity, biodegradability, biocompatibility, antioxidant activity, and antibacterial activity, there is great market potential for

lignin-based formulations. Despite challenges in applying lignin in pharmaceutical industries, the implications of necessary regulatory approvals can serve as a game-changer in lignin-based biopharmaceuticals.

2. Biopharmaceutical relevance of lignin

Lignin's biological activity extends far beyond its structural role in plants. Its antioxidant, antimicrobial, antiviral, and anticancer properties, together with its mechanical robustness and biocompatibility, make it a promising natural polymer for biomedical innovation.[26] The following subsections outline key areas in which lignin and its derivatives contribute to therapeutic and diagnostic applications.

2.1 Antimicrobial potential

Lignin exhibits broad-spectrum antimicrobial properties against bacteria and fungi owing to its phenolic hydroxyl groups and aromatic moieties that disrupt microbial membranes and metabolic processes.[27] For instance, lignin extracted from *Caesalpinia pulcherrima* leaves exhibited antifungal activity against various *Candida* species.[28] Lignin from eucalyptus and spruce has demonstrated antifungal activity against *Aspergillus niger*, with KL exhibiting more potent activity than organosolv lignin.

2.2 Antiviral potential

The antiviral potential of lignin has also been widely recognized. Low-molecular-weight lignin fractions suppress HIV-1 replication by interfering with viral transcription.[29] Lignin from the paper industry was used as a coating material to inactivate herpes simplex virus type 2 (HSV-2) by generating reactive oxygen species.[30] Additionally, lignin has shown effectiveness against herpes simplex virus (HSV-1), with lignosulfonic acid, a lignin derivative, exhibiting antiviral properties against a wide range of viruses.[29] In this context, lignin extracted from *Lentinus edodes mycelium* has demonstrated inhibition against hepatitis C virus infection, and it was also found to inhibit influenza virus.[31] Besides its antiviral properties, lignin has also been investigated for its potential to purify water from viral contaminants. Colloidal lignin particles provide a sustainable solution to viral contamination, as they have the potential to aggregate viruses, facilitating their removal from water.[32]

2.3 Anticancer activity

Besides antimicrobial and antiviral effects, lignin and its derivatives show notable anticancer potential. Lignin and its derivatives have the potential to inhibit cancer cell proliferation and induce apoptosis.[33] Combined with chemotherapeutic agents, lignin-based formulations can enhance the therapeutic efficacy of standard cancer therapies.[34,35] Lignin also exhibits immunomodulatory properties, meaning that it can influence immune system activity to stimulate the body's natural defence mechanisms against tumors. Researchers are investigating the process by which lignin-linked adjuvants can augment the efficiency and effectiveness of many vaccinations or immunotherapy treatments.[36] Overall, the phenolic structure of lignin underlies its diverse biological actions. It donates hydrogen atoms to neutralize free radicals, chelates metal ions to reduce oxidative stress, and interacts with biological membranes and proteins, providing a multifaceted defence mechanism relevant to infection control, oncology, and immunotherapy.

2.4 Tissue engineering

The biocompatibility and mechanical strength of lignin make it an ideal material for use in tissue engineering and regenerative medicine scaffolds or hydrogels that support cell growth and drug delivery. It enhances the scope for various therapeutic applications, including wound healing, bone repair, and soft tissue regeneration.[37,38] As the pharmaceutical industry moves toward more sustainable production practices, lignin is a promising candidate for replacing conventional, petroleum-based materials in various applications.[39]

2.5 Biosensing

Lignin is beginning to gain attention not just due to its structural and bioactive properties, but also due to its functional applications, *e.g.*, in biosensor development. In biosensing, lignin exhibits redox activity because it contains phenolic, quinone, and hydroquinone functional groups. These redox-active moieties enable lignin to participate directly in electron transfer processes at the electrode–electrolyte interface. Through reversible electron–proton transfer reactions, lignin can act as an electron mediator between the electrode surface and the biorecognition element. When an analyte binds or an enzymatic reaction takes place, the local redox environment is altered, which in turn modulates the redox behavior of lignin. This modulation produces measurable changes in current, potential, or impedance, forming the basis for electrochemical signal transduction in lignin-based biosensing systems.[40] These studies highlight that the source and processing of lignin, whether from softwood, hardwood, technical, or nano-particulate sources, are important in defining its reactivity, homogeneity, and biocompatibility.

Together, these findings show that lignin has a wide range of useful biological activities that support its role in many therapeutic and diagnostic areas. Its antioxidant, antimicrobial, antiviral, anticancer, and tissue-supporting properties make it a valuable natural material for medical use. These features provide a strong base for developing lignin-based biopharmaceutical products, which are discussed in the next section.

3. Lignin-based biopharmaceutical products

Lignin is now being actively used as a structural and functional component in the development of several biomedical formulations. Its inherent chemical complexity and tunability allow it to interact synergistically with other biomaterials, forming stable, responsive, and bioactive systems. Whether incorporated into gel-based matrices, dispersed in colloidal systems, or structured into solid-state platforms, lignin supports diverse therapeutic objectives such as drug stabilization, controlled release, wound healing, and tissue repair.

Recent studies have demonstrated the feasibility of lignin-based hydrogels, emulsions, and nanoparticles in both therapeutic and diagnostic contexts.[41,42] These formulations benefit from lignin's antioxidant, antimicrobial, and stabilizing capabilities, which enhance product functionality and therapeutic potential. Additionally, the emergence of technologies such as 3D printing and nanofabrication has opened new avenues for customizing lignin-based biomedical materials.[43] These systems based on their physical form are classified into 3 types: semi-solid formulations, liquid formulations, and solid formulations, which provides an overview of different types of lignin-based biopharmaceuticals (Fig. 2).

3.1 Lignin in semisolid formulations

Semisolid formulations, including creams, gels, ointments, and pastes, play a crucial role in biopharmaceuticals, particularly for topical, transdermal, and mucosal drug delivery (Fig. 3). These formulations comprise a polymer matrix with the drug and excipients dispersed or dissolved in aqueous or non-aqueous bases. Typical formulations consist of a polymer matrix containing the drug and necessary excipients, either dissolved or suspended in aqueous or non-aqueous bases.[44] Lignin has many advantages, such as antioxidant, UV protective, and antimicrobial, which make it a suitable choice in the development of semisolid formulations such as creams, ointments, and gels.[45,46]

In semisolid formulations, lignin is a versatile ingredient due to its ability to act as a gelling agent, contributing to the desirable consistency and texture of the product.[47] Lignin's inherent biocompatibility makes it suitable for skin care and pharmaceutical applications, minimizing the risk of adverse reactions.[48] Lignin's compatibility with other formulation components allows for the production of stable and homogeneous products.[49] When incorporated into semisolid formulations, lignin can enhance the rheological properties, improving spreadability and skin feel.[50] Additionally, it can enhance the stability of proteins, such as enzymes or antibodies, extending the shelf life and efficacy of certain biopharmaceutical products.[48,51] Lignin-based semisolid formulations in skincare may provide antioxidant benefits, helping to protect the skin against oxidative stress and providing anti-ageing effects.[52] Additionally, the antimicrobial properties of lignin could be advantageous in formulations designed to combat skin infections.[53]

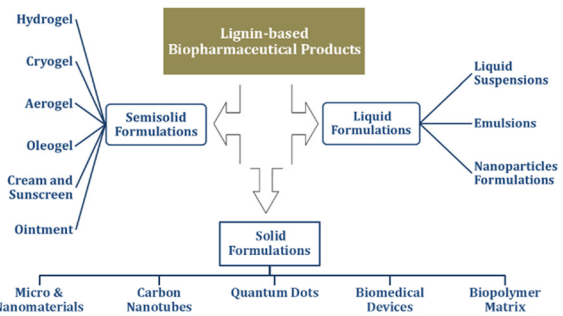

Fig. 2 Types of lignin-based biopharmaceutical products.

Fig. 3 Types of lignin-based semisolid formulations.

Currently, the development of lignin-based semisolid formulations is a promising approach to optimizing extraction processes, ensuring consistency in quality, and addressing challenges related to color and odor.[54] As the industry continues to explore sustainable and innovative ingredients, lignin-based semisolid formulations present a convincing option for formulators seeking effective, eco-friendly, and versatile solutions in skincare and pharmaceutical applications.[55]

3.1.1 Lignin-based hydrogels. The development of semisolid hydrogels involves the use of renewable materials such as cellulose, hemicelluloses, pectin, starch, alginates, lignin, *etc.* Hydrogels are 3D crosslinked networks of hydrophilic polymers, exhibiting viscoelastic or elastic properties. They can be formed from natural or synthetic macromolecules. Out of the renewable resources, lignin is a promising material for the development of functionalized hydrogels.[56] Lignin is a desirable raw material as an adsorbent with substantial sustainability and ecological advantages for hydrogel preparation.[49,57]

Table 2 Lignin-based hydrogels from chemical and physical crosslinking methods

Types of cross-linking	Role of lignin	Matrix	Crosslinker	Ref.
Lignin-based hydrogels by chemical methods	Lignin as a crosslinked unit	Lignin–amine	PEGDGE	61
		Lignin–agarose	ECH	62
		Lignin–xanthan	ECH	63
		Lignin–PVA	ECH	64
		Modified lignin–PVA	ECH	65
		Lignin–Mt–acrylic acid	NMBA	66
		Acrylic acid–OMt–grafted lignin	NEBA	67
	Lignin as a crosslinking agent	PVA	Aminated lignin	68
		PMVE/MA	Lignin and lignin-PEG	69, 70
		Polymerized acrylic acid–PVA	Sodium lignosulphonate	71
Lignin-based hydrogels by physical methods	Lignin as a crosslinked unit	Lignin and hydrophilic PU	N/A	72
	Lignin as a crosslinking agent	Chitosan	Lignin	73
		Chitosan–PVA	Lignin	74

Lignin-based hydrogels can be synthesized through various methods, including interpenetrating polymer networks, crosslinking grafted lignin with monomers, atom transfer radical polymerization (ATRP), and reversible addition–fragmentation transfer (RAFT) polymerization (Table 2).[58] These hydroxyl groups present on the lignin surface act as interfacial crosslinkers and promote hydrogen bonding with other biomolecules. The ionization state of lignin is highly pH-dependent, influencing its physicochemical and biological behavior. At acidic pH, the phenolic groups become protonated, resulting in a decrease in surface charge and an increase in hydrophobicity, which may enhance aggregation and cellular uptake in certain biological environments. Conversely, at basic pH, the phenolic groups in lignin become deprotonated, giving the surface a negative charge. This increases its hydrophilicity and promotes electrostatic interactions with positively charged biomolecules such as proteins and cell surfaces. These changes collectively modify the hydrophilic–hydrophobic balance of the system. This mechanism influences the hydrogel swelling behavior and the release kinetics.[59] The aromatic ring structure of lignin exhibits strong π–π stacking interactions with hydrophobic drug molecules. These weak interactions regulate drug release kinetics.[60]

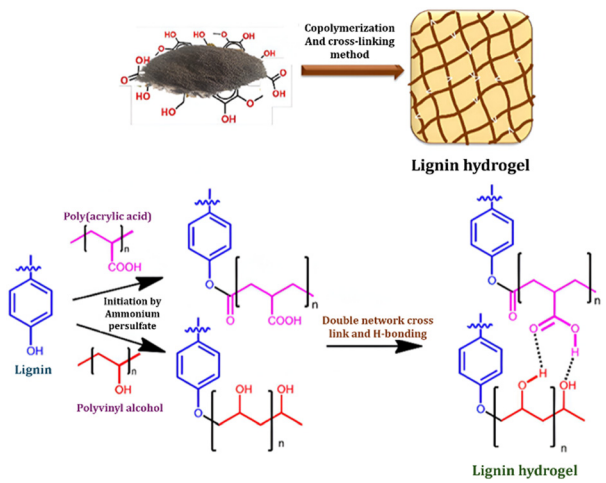

Fig. 4 The schematic diagram for the preparation of the lignin-based hydrogel. Adapted from ref. 57 with permission from the American Chemical Society, *ACS Applied Polymer Materials*, 2022, **4**, 12, 8962–8976. Copyright 2022.

In hydrogel systems based on lignin or natural polymers, and especially for biological use, lignin seldom plays the role of the primary structural matrix. Its role changes based on the nature of the formulation and polymer composition used. In the majority of the formulations, lignin functions as a bioactive additive or secondary crosslinking agent incorporated into polymeric matrices such as poly(vinyl alcohol), chitosan, gelatin, or polyethylene glycol. Through these interactions, lignin enhances the mechanical integrity, moisture-retention capacity, and antioxidant properties of the resulting gel, thereby contributing to its overall stability and functional performance.[75,76] In some systems, lignin acts primarily as an antioxidant and antimicrobial, protecting the encapsulated drug or bioactive principles from oxidation, while supporting wound healing. In specifically designed lignin-rich formulations, lignin may also influence gelation kinetics and viscoelastic behavior when present in substantial amounts.[23,24]

Chandna *et al.* developed a sustainable lignin-based hydrogel incorporating RB@AgLNCs. The lignin-based hydrogel was prepared by crosslinking lignin, PVA, and polyacrylic acid (Fig. 4). This hydrogel coating showed remarkable antifungal activity and maintained effectiveness through photodynamic inactivation, where light-activated photosensitizers (RB) generate reactive oxygen species that damage fungal cells. Its water resistance, transparency, and strong adhesion suggest high potential for biomedical device disinfection.[77]

Notably, lignin-based hydrogels also serve as essential bio-ink components for 3D printing and as structural matrices in wound dressing and scaffold fabrication. While their multifunctional applications are presented in subsequent sections (*e.g.*, section 3.1.5), here we primarily emphasize

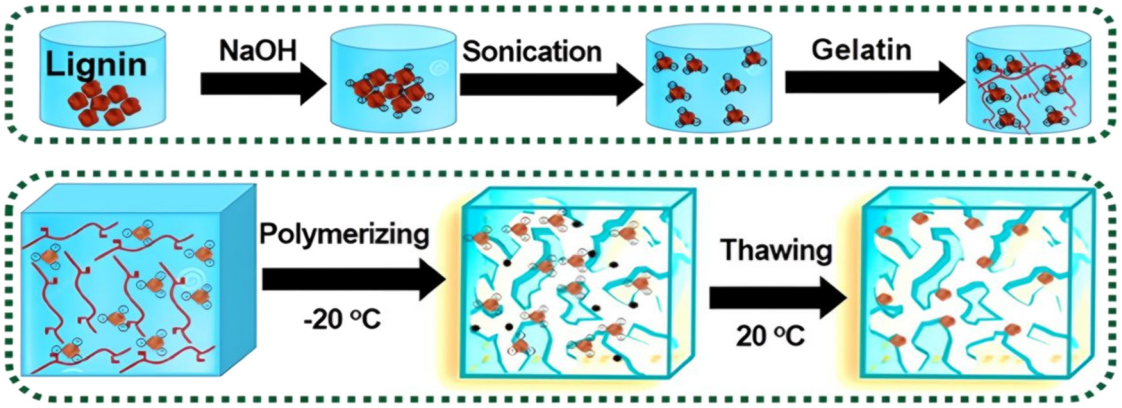

Fig. 5 Schematic illustration of lignin–gelatin cryogel preparation. Lignin was dispersed in aqueous gelatin via alkali-assisted ultrasonication, followed by cryogel formation using glutaraldehyde (GA) as a cross-linker during freezing; residual GA was removed during the thawing step. Reproduced from ref. 78 with permission from the American Chemical Society, *Biomacromolecules*, 2021, **22**, 4110–4121. Copyright 2021.

their semi-solid dosage form characteristics, rheological properties, and fundamental hydrogel-forming behavior. However, hydrogels have poor mechanical strength and rapid drug release capacity, and are very difficult to handle. Lignin-derived hydrogels promote wound healing capacity in a moist environment and act as a scaffold for the regeneration of infected tissue. They are potential candidates for a targeted drug delivery system, biocompatible, and easy to customize for biotherapeutic applications.

3.1.2 Lignin-based cryogels. Lignin-based cryogels are semi-solid biomaterials that are different from hydrogels. Unlike conventional hydrogels, crosslinking of cryogels is made by the cryogelation process and is formed below extreme subzero temperatures.[78] Due to its ability to form a matrix and crosslink in lignin-based biomaterials, lignin provides interconnected supermacroporous gel networks. Lignin-based cryogels have gained attention in the biomedical field, including tissue engineering and drug delivery systems.[79] Abdullah *et al.* developed lignin-*co*-gelatin cryogels. Adding a relatively small amount (0.1–0.2%) of lignin remarkably improved the mechanical properties, shape memory, and injectability of gelatin cryogels.[78] The researchers introduced lignin to cryogels at various concentrations to improve their mechanical properties. Memic *et al.* reported that lignin enhances mechanical efficiency and increases the shape recovery rate, exhibits good antioxidant efficacy, and shows a great inhibitory effect against Gram-positive and Gram-negative bacteria.[80]

Abudula *et al.* developed lignin-based injectable cryogels (lignin-*co*-gelatin cryogels) for biomedical purposes. The developed cryogels were evaluated against surgical site infection-causing pathogens *S. aureus* and *E. coli*.[78] The synthesis of cryogels involves the alkali-assisted ultrasonication and homogeneous mixing of lignin–gelatin solution (Fig. 5). Further, cryogelation was done in the presence of glutaraldehyde as a cross-linker.[78] Lin *et al.* also developed highly porous lignin-formaldehyde cryogels, which have shown enhanced thermal stability and unique thermal insulation.[81] Lignin-derived cryogels are highly sustainable and biobased as compared to petroleum-based conventional cryogels. They are highly porous and lightweight, and have interconnected networks over conventional cryogels which require crosslinkers for building block construction. They also have wide application over biotherapeutics such as water adsorbents, supercapacitors, packaging, and insulation.

3.1.3 Lignin-based aerogels. Lignin-based aerogels have attracted a semi-solid formulation owing to their unique features and a variety of clinical applications, including medical devices, wound healing, drug delivery, and diagnostic tools.[82,83] Aerogels are porous, low-density, semi-solid biomaterials prepared through a sol–gel process. Significant challenges in developing most aerogels include achieving an optimal blend of superior mechanical strength. To address this issue, lignin can be employed as a char-forming agent and structural reinforcer, which helps create aerogels efficiently. It also improves aerogels' fire index diminution and smoke suppression capabilities.[84] Additionally, lignin carbon aerogels have several other uses, such as supercapacitors, adsorbents, catalysts, *etc.*[85] Lignin-based aerogels have various unique properties, such as sustainability, environmental support, high porosity, and excellent heat insulation due to low thermal conductivity, structural strength, and absorptivity. They are also helpful for controlled drug delivery systems and wound dressing due to their excellent absorptivity properties.[82,85] In the context of antioxidant properties, a study by Sanchez *et al.* on a tetracycline-incorporated lignin aerogel showed excellent antimicrobial activity against *S. aureus*.[83] Quraishi *et al.* engineered a non-cytotoxic alginate–lignin hybrid aerogel and reported good cell adhesion, which makes it a potential biomaterial for tissue engineering and regenerative medicine.[86] Lignin-based aerogels have strong potential for future biomedical use. They can be improved to release drugs in a controlled way, support faster wound healing, and act as better scaffolds for tissue repair. Their properties can also be

enhanced through nanomaterial integration and eco-friendly fabrication, making them useful for sensors, diagnostics, and other medical devices.

3.1.4 Lignin-based oleogels. Oleogel is a gel-based semi-solid formulation made by the gelation of oils or fats.[87] Lignin-based oleogels can provide a better option due to their exceptional performance, which contributes to the oleogels' biocompatibility, antimicrobial, and antioxidant properties. Additionally, they could impart mechanical strength and sustainability, which makes the options suitable for biomedical uses. Wu *et al.* developed a lignin–castor oil-based oleogel *via* a reaction between lignin and two silane coupling groups, which showed improved performance and eco-friendly lubricants for the pharmaceutical industry.[87] In this context, it was found that modified lignin (20%) as a thickener could increase the oleogel's antiwear and antioxidation properties. Borrero-López also reported the capacity of KL to be utilized in converting vegetable oils into oleogels to improve their viscosity in the emulsified form. KL nanoparticles were dispersed in castor oil, whose structural elements imparted viscoelastic properties and ensured long-term stability. In this context, acetylated lignin enhanced the rheological properties of the resulting gel dispersion.[88] Based on these findings, lignin-based oleogels can be advanced further for drug delivery, wound protection, and other biomedical uses. Their structure can be adjusted to improve stability, flow behavior, and controlled release. Future studies may combine lignin with active compounds or nanoparticles to create multifunctional therapeutic gels. With cleaner processing and better design, these oleogels could become dependable materials for clinical and pharmaceutical applications.

3.1.5 Lignin-based 3D printing dressing. This section presents one of the other application extensions of lignin-derived hydrogels described in section 3.1.1. In this context, hydrogels function as printable, shear-thinning biomaterial inks, where their physical state enables layer-by-layer deposition and structural fidelity. Here, the focus is placed on their performance and therapeutic role when formulated into 3D printed wound care systems, rather than the hydrogel network properties discussed previously. The applications of 3D printing have gained attention in terms of performance, economy, and the environment.[89,90] Lignin-based 3D printing materials can be developed by using lignin as an additive that can be used for novel drug delivery purposes and tissue engineering. They can impart quality features such as electrical conductivity and bioactivity, and their sustainable manufacturing can provide lignin as a biomaterial with desired mechanical properties, especially for electronic, optical, and medical device applications.[47,89,90] The latest 3D printing technology can overcome the demand for tooling and machines. Lignin can be blended directly into 3D printing items or modified with various thermoplastic materials.[89] The three-dimensional structure of lignin biomaterials can provide the necessities, which are commonly applied for antioxidant and antimicrobial applications.[90] The various natural biomaterials provide control over oxidative stress and induce their healing. Recently, Domínguez-Robles *et al.* developed a lignin-based 3D-printed wound dressing loaded with curcumin and D-panthenol and it showed promising healing results on a Wistar rat animal model.[47] Another study used lignin's antioxidant capability to design and prepare meshes and capsules for wound dressing potential (Fig. 6).[91] Additionally, another example of wound dressing and tissue engineering reported by Jaiswal *et al.* is a carrageenan–lignin–silver nanoparticle (AgNP)–$MgCl_2$-based polymeric gel, which was prepared by cross-linking of the carrageenan matrix with $MgCl_2$ divalent cations, and it exhibited cellular ingrowth and vascularization.[92] While lignin-based hydrogels and 3D printing dressings share material origin, their discussion in separate sections reflects differences in dosage form and translational application. The conventional 3D printing materials, such as polylactic acid (PLA), acrylonitrile butadiene styrene (ABS), and other petroleum-based polymers, are generally considered biocompatible; however, they may still induce inflammatory responses in certain biomedical or skin-contact applications. In contrast, lignin-derived printing materials offer inherent antioxidant activity and reduced immunogenicity, making them promising alternatives, although extensive research and optimization are still required to fully realize their potential.

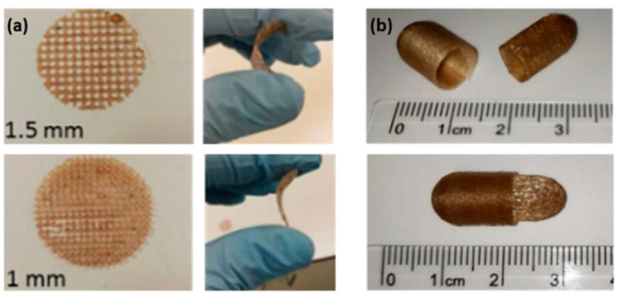

Fig. 6 3D printing (a) meshes and (b) oral capsules. Reproduced from ref. 91, J. Domínguez-Robles *et al.*, *Pharmaceutics*, 2019, **11**, 165, under the terms of the Creative Commons CC-BY 4.0 licence.

3.1.6 Lignin-based creams. Recent studies suggested that lignin has become an alternative biomaterial for preparing various semi-solid cosmetic formulations.[50] Lignin's various chromophores, the covalent C–C double bonds such as carbonyl groups and aromatic systems, impart the UV-absorption properties. It can be incorporated into various types of creams and sunscreens to provide advantages such as UV protection, protection against free radicals, an improved humectant nature, and a sun protection factor (SPF)-boosting effect.[50,93] Besides its biocompatibility, it has been studied and analyzed in an *in vivo* model of zebrafish (*Danio rerio*), and this study revealed that it can be utilized as an alternative sunscreen ingredient.[94]

Generally, lignin-based creams are prepared as oil-in-water (O/W) emulsions, where lignin is dispersed in the aqueous phase prior to emulsification. Normally, lignin is dissolved in

an alkaline aqueous solution (pH 7.5–8.5) and then subjected to ultrasonication. This aqueous lignin phase is heated to 70–75 °C to maintain the same temperature as the oil phase (*e.g.*, fatty alcohols, esters, and emollients), which is heated to 70–75 °C. The two phases are then mixed under homogenization (4000–10 000 rpm) to form the emulsion. To stabilize the cream structure, slow cooling under continuous stirring is needed. The aromatic and phenolic groups of lignin interact with emulsifiers and polymeric thickeners through hydrogen bonding and π–π interactions, contributing to viscosity, SPF enhancement, and antioxidant stability. Critical process parameters that influence the texture, spreadability, and uniformity of lignin dispersion include pH (typically maintained between 5.0 and 6.0 for skin compatibility), homogenization speed, and cooling rate.

In one of the studies conducted by Antunes *et al.*, lignin was extracted from sugarcane bagasse. The extracted lignin was utilized to prepare a multifunctional blemish balm (BB) cream. The experimental *in vitro* and *in vivo* results predicted its broad-spectrum UV protection, cytotoxicity, skin allergenicity, genotoxicity, and acute skin irritation, which was safe for topical applications.[50] Additionally, lignin-based sunscreens have gained enormous interest in developing cosmeceutical formulations.[14] One of the studies exhibited that lignin has enhanced synergistic properties with the marketed sunscreen. The resulting formulation has boosted the SPF with good sunscreen performance.[93] Conclusively, lignin has a large number of phenolic groups in its structure, which is responsible for its anti-inflammatory and skin-calming effects. Consequently, it showed potential benefits for acne, dermatitis, sunburn, redness, and irritation in biotherapeutic applications.

3.1.7 Lignin-based ointments. Lignin could be a natural alternative raw material for developing ointments, which are oil-like semi-solid formulations applied as emollients for dermal applications. An ointment base is generally obtained by combining a polymeric matrix of different materials.[95,96] The purified lignin in the ointment base can be mixed by homogenization, and it can impart therapeutic and protective benefits for topical applications. Several other advantages, such as antioxidants, moisturization, and skin-caring biocompatibility, have also been reported. Lignin-based ointments are normally prepared using anhydrous or emulsion-type ointment bases. Priorly, the ointment base (*e.g.*, petrolatum, lanolin, plant oils, or wax blends) is molten at 60–70 °C. Lignin is then incorporated gradually under continuous stirring, followed by homogenization to achieve uniform dispersion. The active compound can be either dissolved in the oil phase or pre-adsorbed onto lignin particles (using sonication) before blending, enabling controlled release in drug-loaded formulations. The formulation develops a stable semi-solid matrix that enhances hydration, antioxidative protection, and antimicrobial activity due to the interaction of phenolic groups of lignin with lipid chains and polymeric excipients. Critical parameters include the particle size of lignin, mixing rate, base composition ratio, and cooling profile, which collectively influence occlusion, spreadability, and therapeutic performance on the skin.

One such study reported by Mahata *et al.* describes the development of a lignin-*graft*-polyoxazoline conjugated triazole-based efficient ointment having anti-inflammatory solid activities due to lignin's inherent antioxidant and antimicrobial properties. The study was carried out on biofilm and animal models infected with *Pseudomonas aeruginosa* HW01-induced burn-wound healing.[95] The aqueous-based gel has been incorporated with lignin and exhibited better rheology and drug loading. Further, the *in vivo* study suggested its safe use in skin burns to avoid secondary infections.[97] Lignin-based ointments can be improved further for wound care and controlled drug delivery. Small changes in lignin size, surface treatment, and base composition can enhance spreadability and release behavior. Adding bioactive agents or nanoparticles may strengthen antimicrobial and healing effects. With simpler and greener processing, these ointments can become reliable options for future topical therapies.

3.2 Lignin-based liquid formulations

Nanoformulations in biopharmaceuticals are particularly used for the delivery of poorly water-soluble drugs, biological macromolecules, and nanoparticle-based therapeutics. These formulations consist of finely dispersed drug particles in a liquid medium to prevent sedimentation and aggregation. They offer several advantages, such as ease of administration, rapid action, and avoiding difficulty in swallowing.[98,99] The engineering of lignin properties has gained significant attention due to its potential for wide-range applications. For a material to be suitable for industrial use, it must be widely available and cost-effective, exhibit good technological performance, and possess low toxicity. Lignin fulfils many of these criteria and has been utilized in various liquid formulations, such as emulsions, suspensions, and formulations, highlighting its versatility. These properties allow lignin-based liquid systems to serve as carriers for therapeutic molecules, excipients in dermatological and nutraceutical preparations, and stabilizers in injectable formulations.

3.2.1 Lignin-based liquid suspensions. Lignin-based suspensions developed by organic solvent–water binary combinations favour the solvation of both hydrophobic and hydrophilic groups of lignin. Water is chosen as a secondary and primary solvent based on its capacity to solubilize lignin, environmental impact, and recyclability. Commonly used primary solvents are generally toxic, flammable organic derivatives, and also exhibit low compatibility in the scaling-up of industrial processes. Emerging technologies focus on novel green alternatives such as ethanol, *p*-toluene sulfonic acid, and deep eutectic solvents.[100–102] These suspensions are increasingly used in nanomedicine, antimicrobial sprays, and topical biopharmaceuticals.[100] For example, Paul *et al.* developed ethanol–water-based lignin nanospray solutions

Fig. 7 The schematic representation of the synthesis of the lignin nanospray using lignin. Reproduced from ref. 103 with permission from The Royal Society of Chemistry, *Journal of Materials Chemistry B*, 2021, **9**, 1592–1603, Copyright 2021.

using a solvent–antisolvent method (Fig. 7), which demonstrated potent antimicrobial activity and applicability in wound disinfection.[103] These nanospray formulations are relevant to biopharmaceuticals as they can be adapted for wound-healing sprays, antifungal bio-preservatives, and localized antimicrobial drug delivery in clinical settings. The cosmetic sector is exciting since it makes it easier to prepare formulations directly without requiring the time-consuming and energy-intensive separation of LNPs. Sunscreen formulas that are environmentally friendly and have varying SPF levels were created using Kraft-colloidal lignin nanoparticles (K-cLNPs) and eco-friendly dimethyl isosorbide (DMI). Additionally, DMI eliminated the need for chemical and physical UV filters as microplastic boosters by dissolving water-insoluble UV filters due to its high solvent capacity. Biological studies using human skin equivalents (HSEs) and HaCaT keratinocyte cell lines confirmed that these developed cLNPs and sunscreen formulations are non-cytotoxic and non-genotoxic, offering effective protection against UV-A-induced skin damage.[104] Lignin-containing suspensions reduce the need for synthetic surfactants and stabilizers, improving stability and enabling sustained release in biopharmaceuticals. Their tunable chemistry allows safer, skin-friendly liquid formulations with improved solvent compatibility. With better control over solvent systems and dispersion, lignin suspensions hold strong potential for future therapeutic and personal-care applications.

3.2.2 Lignin-based emulsions. Emulsions have been extensively utilized for protecting, transporting, and delivering functional chemicals. Lipophilic bioactive molecules can become more bio-accessible when transported in oil-in-water emulsions. Selecting an appropriate emulsifier is one of the most essential steps in synthesizing stable emulsions. There is growing interest in identifying natural emulsifiers for sustainable formulation development. Biodegradable biomolecules such as phospholipids, proteins, and polysaccharides have long been used to stabilize emulsions. Recently, lignin has also attracted attention as a natural emulsifier and has been successfully employed in emulsion synthesis.[105,106]

Lignin-based emulsions can be used as a template for the synthesis of polymers with porous architectures, such as fuel emulsions, organic carriers, and others.[107,108] Emulsion investigations were conducted using LS and KL with varying

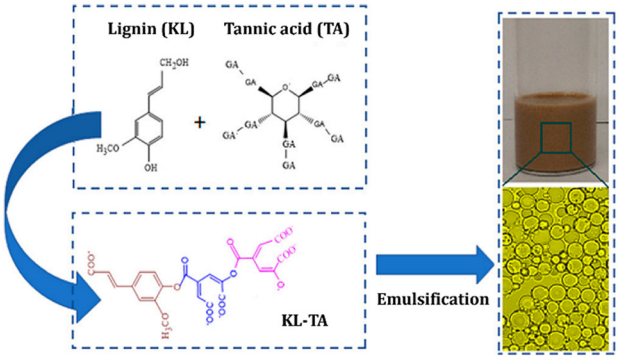

Fig. 8 Tannic acid and KL as a stabilizer for oil-in-water emulsions. Reproduced from ref. 113 with permission from the American Chemical Society, *ACS Sustainable Chem. Eng.*, 2019, **7**, 2370–2379, Copyright 2018.

molecular weights. However, their use in emulsions is restricted due to LS's high sulfur content and KL's poor solubility.[109,110] KL shows low surface activity and exhibits a hydrophilic character at high pH. To overcome the hydrophobicity and low charge density of KL, it was reacted with tannic acid under alkaline conditions. KL–tannic acid acts as a green emulsifier/stabilizer for oil-in-water emulsions (Fig. 8).[111] The bioavailability of lipophilic therapeutic molecules such as curcumin, essential oils, and hydrophobic anticancer agents can be enhanced through encapsulation within lignin-based systems, where lignin-stabilized emulsions improve their dispersion, stability, and sustained-release behavior. The research was carried out to determine the behaviour of emulsions stabilized by polymer-grafted lignin particles, in which lignin particles were grafted by RAFT using two distinct polymers of polyacrylamide and polyacrylic acid.[112] Technological characteristics of lignin as an emulsifier were determined to add value to this biopolymer for water purification, water treatment, food, cosmetic, paint, biomedical, chemical, and agricultural industries.[107,113] In another study, the reactor formed stable oil-in-water emulsions.[114] Recently, researchers looked at how well water-soluble carboxymethylated lignin produced stable kerosene in a water emulsion. They observed that lignin particles with a high degree of substitution could keep emulsions reasonably stable throughout various conditions.[115] Lignin-based emulsifiers can lead to safer and more sustainable emulsion systems for medical, cosmetic, and industrial use. Chemical modification of lignin can further improve its surface activity and compatibility with different oils and solvents. Better control of particle size and charge may enhance emulsion stability and drug-loading ability. These advances can support future applications in therapeutic delivery, functional foods, and eco-friendly formulations.

3.2.3 Lignin-based nano-formulations. There are two types of lignin-based nanocarriers: lignin nanoparticles (LNPs) and lignin nanocapsules (LNCs). While both possess a spherical shape, LNPs consist of a solid lignin matrix in which the

active ingredient is uniformly distributed. LNCs feature a hollow lignin shell encapsulating either liquid or solid substances within.[116] LNPs are formed *via* nanoprecipitation or dissolving lignin in an organic solvent and water.[117] To avoid using organic solvents, lignin nanoparticles (LNPs) can be synthesized by diluting a concentrated aqueous solution containing a hydrotropic agent, typically an ionic organic salt that facilitates lignin dissolution. This method is considered environmentally friendly, as the hydrotropic agent can be efficiently recovered and reused.[118] The water phase or a volatile organic solvent can dissolve lignin, and the oily phase consists of active ion ingredients. LNCs were synthesized from oil–water emulsions by using simple ultrasonication (Fig. 9).[119–121] LNPs and LNCs have demonstrated the efficient encapsulation of antibiotics, anticancer drugs, and photosensitizers, showing their role in controlled drug release, antimicrobial wound coatings, and photodynamic therapy. Ultrasonic waves lead to cavitation by generating high temperatures and pressure. These conditions enhance π–π stacking interactions among lignin's aromatic moieties and facilitate the formation of intermolecular hydrogen bonds.[120] Additionally, it protects drugs from oxidative degradation, enhances their shelf life, and increases cell and skin protection. Lignin-based nanocarriers can be further refined for targeted delivery, improved penetration, and safer dose control. Adjusting particle size, surface charge, and shell composition may strengthen drug protection and release profiles. Their natural stability and compatibility also open opportunities in vaccines, topical therapies, and light-activated treatments. Continued development could position these nanocarriers as reliable, sustainable platforms for advanced biomedical applications.

***In vivo* metabolism and biosafety considerations of lignin-based liquid formulations.** After administration, lignin undergoes partial biodegradation through oxidative and enzymatic pathways involving peroxidases and gut microbiota. These processes convert lignin into phenolics, which are further transformed into enterolignans such as enterolactone and enterodiol, known to exhibit antioxidant and anti-inflammatory effects.[122] In animal models, lignin nanoparticles have shown low cytotoxicity, minimal immunogenicity, and safe renal clearance when particle size and molecular heterogeneity are well-controlled. The uniform size and purification of lignin nanoparticles ensure essential parameters for safe biopharmaceutical use.[123]

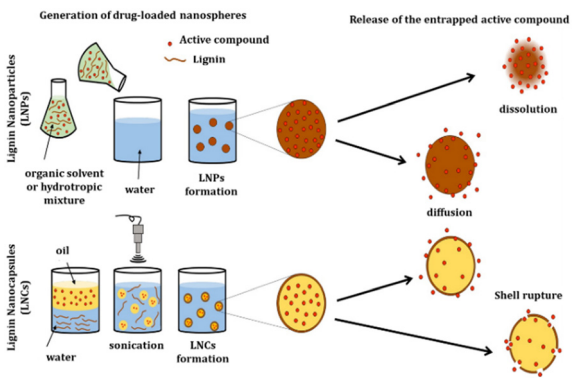

Fig. 9 Synthesis of lignin-based nanocarriers. Reproduced from ref. 121, Gigli *et al.*, *Frontiers in Plant Science*, 2022, **13**, 976410, under the terms of the Creative Commons CC-BY 4.0 licence.

3.3 Lignin-based solid formulations

Solid formulations have gained significant attention in biopharmaceutical applications due to their ability to enhance therapeutic agents' stability, efficacy, and patient compliance. They offer better shelf life and reduced susceptibility to environmental degradation.[124] Advances in formulation science have also enabled the integration of novel biomaterials, including biopolymers such as lignin, into solid dosage forms, enhancing biocompatibility and enabling eco-friendly drug delivery platforms. These discoveries are opening new opportunities for using lignin in both materials science and biomaterials development. Different types of lignin-based solid formulations have been developed for pharmaceutical applications such as drug delivery, bioimaging agents, *etc.*

3.3.1 Lignin-based micro and nanomaterials. Lignin nanomaterials have garnered global interest due to their renewability, low cost, and desirable physical properties. Various phenolic composites, including those modified with nanocellulose and nanolignin, are produced through advanced synthesis methods. These lignin-based nanomaterials, such as KL, have diverse applications in biomedical fields, including tissue engineering and drug delivery, as well as in surface coatings and microfluidic devices.[125] Lignin-based micro- and nanoparticles are mostly spherical shapes with hollow or solid structures and are particularly promising in biomedicine. These particles, typically 100 nm to 1000 nm, can entrap or disperse active substances like drugs, genes, and metal nanoparticles. Recently, there has been significant interest in developing lignin nanoparticles for antimicrobial applications and drug delivery systems.[27,42,126] Several methods for preparing drug-loaded lignin nanoparticles have been reported, including precipitation, dialysis, solvent exchange, and ultrasonic radiation. Recent studies have shown lignin-derived nanomaterials' strong potential in biomedical applications, especially for poorly water-soluble drugs and genes.[53,127] Drug incorporation methods include entrapment, encapsulation, physical adsorption, and chemical linkage. Nanoparticles can be functionalized for stimuli-responsive behaviour, including pH, temperature, magnetism, or active targeting, to improve accumulation and therapeutic efficacy. Thus, optimizing lignin nanoparticles' properties is crucial for enhancing their effectiveness in drug delivery.[35]

Many drugs face limitations in clinical use due to poor water solubility and adverse effects on normal tissues. To address this, improving targeted delivery and tissue penetration is crucial. Liu *et al.* developed folic acid–polyethylene glycol–alkaline lignin conjugates (FA-PEG-AL) to

create targeted nanoparticle vehicles for delivering hydroxyl camptothecin (HCPT).[128] Chen *et al.* demonstrated that various lignin types effectively dissolve poorly water-soluble drugs like doxorubicin and gatifloxacin in a hydrotropic system. This method achieves 90% drug encapsulation efficiency, making it suitable for scalable, high-yield production of drug-loaded lignin nanoparticles.[129]

Figueiredo *et al.* prepared lignin nanoparticles complexed with iron and magnetic Fe_3O_4-infused lignin nanoparticles (Fe_3O_4-LNPs) to assess their potential in nanomedicine. Fe_3O_4-LNPs showed the most promising results for cancer therapy and diagnosis. While high concentrations of these nanoparticles can cause cytotoxicity and haemolysis, no significant toxicity was observed at concentrations up to 100 mg mL^{-1}, suggesting their suitability for nanomedicine with controllable concentration and time-dependent effects.[130] Dai *et al.* loaded *trans*-RSV (insoluble anticancer drug) with Fe_3O_4 into lignin nanoparticles for passive and magnetic targeting. In mice, AL/RSV/Fe_3O_4 NPs retained more *trans*-RSV in tumours than free *trans*-RSV. It was found that the developed NPs effectively inhibited tumor growth and improved survival rates, with the latter benefiting from sustained drug release, optimal particle size, magnetic properties, and superior biocompatibility and dispersibility.[131] Figueiredo *et al.* conjugated lignin nanoparticles with Asp-Ser-Ser (DSS) polypeptide, known for its cell-penetrating properties, to improve interactions between cells and lignin nanoparticles. The DSS polypeptides were chemically conjugated to carboxyl groups on lignin nanoparticles using EDC/NHS coupling chemistry in a mild buffer, preserving loading efficiency. The developed system improved the dissolution rate and stability under tumor-like conditions, enhancing cellular uptake and antiproliferative activity in both 2D and 3D tumor models.[130]

Nanoparticle formulations can enhance drug bioavailability and promote quick oral absorption of poorly soluble drugs. Lignin, which is insoluble in acidic solutions but soluble under alkaline conditions, holds potential for targeted drug release in the intestine. Alqahtani *et al.* developed a formulation for curcumin by cross-linking lignin in a citrate buffer. This achieved excellent stability under gastric conditions and sustained release in simulated intestinal fluid. This formulation improved curcumin permeability and bioavailability compared to the curcumin suspension.[132] Lignin nanoparticles demonstrate enhanced thermal performance and stability across a broad pH range and exhibit antiproliferative effects against cancer cells. They are also incorporated into cosmetics, particularly sunscreens, for UV protection. Lignin nanomaterials can be further refined for precise targeting, improved penetration, and safer delivery of difficult-to-solubilize drugs. Combining lignin with peptides, metals, or polymers may expand their use in cancer therapy, imaging, and oral drug systems. These advances position lignin nanomaterials as strong candidates for future biomedical and pharmaceutical technologies.

3.3.2 Lignin-based carbon nanotubes. Lignin-based carbon nanotubes (CNTs) represent an innovative intersection of sustainable materials science and advanced nanotechnology. Lignin-based CNTs are CNTs synthesized from lignin as a carbon precursor using chemical vapour deposition and pyrolysis methods. By leveraging lignin's aromatic-rich structure and natural abundance, these approaches enable the formation of CNTs with high mechanical strength, electrical conductivity, and thermal stability. Such properties make lignin-derived CNTs suitable for diverse applications, including energy storage, environmental remediation, and biomedical use. This approach promotes sustainability and potentially minimizes production costs, marking a significant advancement in both materials science and green technology.[133]

These materials benefit from lignin's renewable origin and inherent surface functionality, which differentiates them from conventionally synthesized CNTs derived from fossil-based precursors. Compared to conventional CNTs, lignin-based CNTs often exhibit higher surface functionality and defect density, thereby enhancing dispersibility and interfacial interactions. These features are particularly advantageous for biomedical applications such as drug delivery, imaging, and tissue engineering. With their high surface area and potential for targeted drug release, lignin-based CNTs offer new possibilities for improving therapeutic efficacy and precision. Additionally, their unique properties, including antioxidant and antimicrobial effects, are significantly effective in wound healing and infection control. This combination of sustainability and performance positions lignin-based CNTs as a ground-breaking solution for developing next-generation biopharmaceutical products.[134,135] However, lignin-based CNTs have promising applications in drug delivery systems, tissue engineering, and biosensor development. They also have a lower environmental impact, generating fewer greenhouse gases, promoting a circular bioeconomy, and reducing waste compared to conventional CNT production.

3.3.3 Lignin-based carbon dots. Lignin-based carbon dots are emerging as a promising innovation in the biopharmaceutical field, leveraging the unique properties of quantum dots while incorporating the sustainable advantages of lignin. Quantum dots, known for their size-tunable optical properties and high photostability, can be engineered from lignin to create biocompatible nanoparticles with enhanced fluorescence and imaging capabilities.[136,137] These lignin-based carbon dots are particularly valuable for applications in drug delivery and diagnostics, where their ability to emit specific wavelengths of light allows for precise tracking and visualization of therapeutic agents within biological systems. Additionally, incorporating lignin can improve biocompatibility and reduce the toxicity of quantum dots, making them suitable for *in vivo* applications. Their potential use in targeted therapy, molecular imaging, and biomarker detection highlights the transformative impact of lignin-based carbon dots in advancing biopharmaceutical technologies.[138,139]

Chen *et al.* produced lignin-based carbon dots through hydrothermal treatment with an H_2O_2–Fe^{2+}/Fe^{3+} system for bioimaging. The optimal carbon dots exhibited strong blue photoluminescence at 430 nm when excited at 320 nm and maintained stable fluorescence intensity for over 100 minutes, outperforming CdTe quantum dots in stability.[140] Niu *et al.* developed lignin-based carbon dots for cellular imaging. These carbon dots formed through molecular aggregation during dialysis, averaging 2.4 nm in diameter. After assessing potential cytotoxicity, carbon dots were tested for their cellular imaging capabilities in HeLa cells. The carbon dots were in cells within 1 hour, and they could be observed in the cell nuclei after three hours *via* fluorescence.[141]

Rai *et al.* developed carbon dots from LS lignin for cellular imaging and drug delivery with a high quantum yield of up to 47.3%. The synthesis process involved microwave irradiation followed by reduction with $NaBH_4$. The presence of sulfur in LS enhanced fluorescence stability and the quantum yield.[138] Myint *et al.* synthesized fluorescent carbon dots (CDs) from KL using the compressed liquid CO_2 antisolvent method, which involves carbonization and oxidation. These dots exhibited bright yellow fluorescence under 458 nm excitation. CDs showed no cytotoxicity to HeLa cells at a 500 μg mL^{-1} concentration after 48 hours and maintained strong fluorescence.[139] Lignin-based quantum dots can be advanced for safer bioimaging, real-time tracking, and combined imaging–therapy systems. Fine control over their size, surface groups, and emission range may enhance brightness and targeting accuracy. Their low toxicity also supports future use in *in vivo* diagnostics, biosensing, and image-guided drug delivery. These developments position lignin-derived quantum dots as promising tools for next-generation biomedical technologies.

3.3.4 Lignin-based pharmaceutical formulations and biomedical devices. Biomedical devices play a pivotal role in the development and application of biopharmaceuticals, enabling precise delivery, controlled release, and improved therapeutic efficacy of biologically active compounds. These devices encompass many tools, including implantable drug delivery systems, biosensors, microneedles, wound dressings, and tissue scaffolds (Fig. 10).[142] Lignin-based biomaterials are increasingly used due to their affordability and simple synthesis processes, making them suitable for science, engineering, and medical applications. They have high carbon content and thermal stability and are biodegradable, with antioxidant and antimicrobial properties. These qualities enable their use in sensors, targeted drug release, and memory materials. They are also biocompatible and less harmful to cells, showing photoluminescence properties useful for biomedical imaging.[143] Oral solid dosage forms (tablets or pills) are widely used solid dosage forms favoured by patients. Excipients play a crucial role in their production. Common excipients include cellulose, microcrystalline cellulose, starch, and xylitol, which improve disintegration and drug

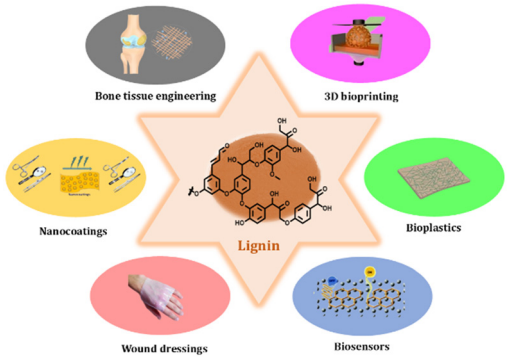

Fig. 10 Different types of lignin-based biomedical devices.

bioavailability. While lignin is gaining attention as a material for nano- and micro-scale drug delivery, its potential as an excipient in solid dosage forms has been less explored.[144]

Domínguez-Robles *et al.* utilized lignin as a vehicle for manufacturing drug-containing solid oral dosage forms. Their findings indicated that incorporating lignin could potentially alter the pattern of drug release. Additionally, the antioxidant properties of lignin could effectively protect the active ingredients from oxidative degradation within the formulation.[144] Pishnamazi *et al.* found that Alcell lignin enhances the compressibility of microcrystalline cellulose/lactose monohydrate composites, improving flowability during roll compaction. It was observed that incorporating lignin as an excipient reduces disintegration time and accelerates drug release rates in aspirin pills. This is attributed to lignin's amorphous structure and unique interaction with aspirin, enhancing bioavailability.[145] On the other hand, carboxylated lignin decreases pill hardness and accelerates the disintegration and release rates of paracetamol due to reduced interaction with the drug. Lignin-containing solid oral dosage forms also exhibit controlled release behaviour under simulated intestinal conditions, showcasing potential in pharmaceutical formulations.[146] However, the biological performance of lignin in pill formulations requires further investigation across different therapeutic applications. In biomedical imaging, essential for detecting and treating diseases like cancer, lignin-based biomaterials play a role in photodynamic and photothermal therapies. They are synthesized with metal ions, carbon dots, or porphyrins in several steps to improve their functionality.[137,147] In photodynamic therapy, lignin acts as a carrier or matrix for photosensitizers, enabling light-triggered reactive oxygen species generation. In photothermal therapy, lignin-based composites convert absorbed light into localized heat for therapeutic action when combined with suitable photothermal agents. Native lignin exhibits intrinsic autofluorescence mainly in the UV-visible region due to its aromatic structure. The near-infrared fluorescence used for bioimaging generally arises from incorporated photosensitizers or fluorescent dyes within the composite

system, while lignin functions as a biocompatible carrier.[148] In addition, the redox activity and surface functionality of lignin support its integration into biosensing platforms, where changes in optical or electrochemical signals can be used for analyte detection. Lignin-based materials can be further developed for safer and more efficient drug-delivery devices, microneedles, and wound-care systems. Their tunable chemistry may allow better control of release rates, mechanical strength, and imaging responses. Combining lignin with metals, polymers, or fluorescent agents could expand its use in biosensing and image-guided therapies. These improvements can help establish lignin as a reliable and sustainable component in future biomedical devices.

3.3.5 Lignin-based biopolymer matrix. This section represents another application extension of lignin-derived materials as described in sections 2.1.1 and 2.1.5. This section focuses on the role of lignin as a structural biomaterial for scaffold fabrication and tissue regeneration. A biopolymer matrix is a continuous polymeric framework that serves as a supporting network, enabling the incorporation of active materials for enhanced functionality. Lignin-based biopolymer matrices are emerging as a promising frontier in biopharmaceuticals, leveraging lignin's abundance. Known for its structural strength and biocompatibility, lignin can be chemically modified to enhance its properties, making it an attractive candidate for various applications, including drug delivery systems (as discussed in the previous sections), tissue engineering scaffolds, and wound dressings. The intrinsic polymer chemistry of lignin offers the same essential advantages, but the resulting biomaterial varies in performance depending on how lignin is processed as a hydrogel, printable bio-ink, or as a fibrous scaffold matrix.

Electrospun fibres, known for their high surface area-to-volume ratios, are used in tissue engineering scaffolds for cell cultivation.[149] Lignin, used as a polymeric additive in electrospinning, faces challenges in forming homogeneous and elastic nanofibers due to its incompatibility with nonpolar polymers like polylactic acid (PLA), polyhydroxybutyrate (PHB), and polycaprolactone (PCL).[102] To address this, researchers like Kai *et al.* have developed methods to chemically graft polymer chains onto lignin, improving its compatibility with polymer matrices. Their lignin-graft-PLA copolymer, for example, creates well-dispersed, homogeneous nanofibers with diameters of 350–500 nm. These fibres show good compatibility with PLLA, antioxidant activity, and biocompatibility with various cell types. Other lignin-containing polymer nanofibers have also been developed, including combinations with PHB, PCL, and PMMA. Liang *et al.* have reported a PCL–lignin nanofiber membrane with intrinsic antioxidant activity, excellent mechanical properties, low cytotoxicity, and anti-inflammatory effects, showing promise for osteoarthritis treatment as an alternative to traditional antioxidants.[150]

Bone regeneration scaffolds, crucial in tissue engineering, greatly rely on mechanical stability. Rekola *et al.* developed a metal-free, fibre-reinforced composite bone material by heat-treating wood inspired by the porous structure of wood and bone. This treatment improved the osteoconductivity of the artificial implants, demonstrating lignin's good biocompatibility.[151] Additionally, recent research found that unmodified PCL and lignin can form a uniform solution in chloroform/DMF, creating mineralized, hydroxyapatite-coated fibres through electrospinning. Lignin's reactive phenolic and aliphatic hydroxyl groups help in the chelation of Ca^{2+}, crucial for hydroxyapatite formation, enhancing osteoblast adhesion and proliferation, making this platform a promising bone regeneration material.[152] Reesi *et al.* synthesized a lignin-based nanofibrous dressing with arginine for wound healing, which mimics the extracellular matrix and accelerates wound closure *in vivo*. The combined antibacterial and antioxidant properties of lignin and controlled arginine release boost nitric oxide levels and collagen deposition, further enhancing wound healing properties.[153] Lignin-based biopolymer matrices can be further optimized for stronger, more cell-responsive scaffolds in tissue repair. Simple chemical modifications may improve fibre formation, mineralization, and compatibility with other biomedical polymers. Their natural antioxidant and antimicrobial traits also support future use in smart wound dressings and regenerative implants. With better control of the structure and processing, lignin-derived matrices could become reliable, sustainable alternatives to conventional scaffold materials.

Lignin appears in multiple dosage form categories across this review; each section highlights a distinct functional state (semi-solid hydrogel, printable formulation, or scaffold matrix), supporting the rationale of classifying biomaterials based on their physical form and administration characteristics (Table 3). The lignin-derived biopolymer matrix inhibits bacterial growth, fungal colonization, and the formation of biofilms. Thus, there is a wide range of applications in food packaging films, biomedical scaffolds, and wound dressings, replacing chemical-based biopolymer matrices.

3.4 Mechanistic insights of lignin formulations

Numerous researchers have investigated lignin-based biomedical formulations, including hydrogels, polyurethanes, nanoparticles, and carbon nanotube (CNT) composites; nevertheless, most studies have primarily focused on synthesis routes and formulation approaches. However, there is limited discussion about the underlying mechanisms involving lignin's performance in these systems. A mechanistic understanding of lignin's role in such formulations is critical, as its functional groups vary widely depending on the chemical structure and source.

Phenolic hydroxyl groups in lignin contribute to hydrogen-bonding or covalent crosslinking.[75] In hydrogels, phenolic hydroxyl groups of lignin act as interfacial crosslinkers by establishing hydrogen-bonding networks with hydroxyl and

amino groups in polymers such as PVA and chitosan. This is accompanied by π–π stacking and hydrophobic interactions of lignin's aromatic domains, thereby enhancing interfacial adhesion.[160,161] These studies show that the functional contribution of lignin goes beyond mere coloration or stabilization, but actively affects the nature of the bioactivity and mechanical integrity of such hydrogels.

In general, lignin-based composite biogels exhibit enhanced fatigue resistance, toughness, and adhesion to the substrate due to the interaction of the aromatic and aliphatic components of lignin with the polymeric framework of the composite. This observation highlights the importance of the lignin type, source, and functionalization for the mechanical and biological properties of the resulting products.[162,163] In addition to systems based on gels, lignin has also been incorporated into chitosan composites and lignin–cellulose complexes for other biomedical-relevant applications where its bioactive groups and interfacial interactions contribute to beneficial functional effects.[162,163]

In CNT composites, lignin acts as a dispersant and facilitates interfacial charge transfer. Due to its aromatic rings, it attaches to the nanotubes through π–π interactions, which helps keep the formulation dispersed and stable.[164] In polyurethane systems, lignin plays a different role; it can act as a chain extender or a reactive filler. Its aliphatic hydroxyls and aromatic rings help in making the material tougher,

Table 3 Examples of different types of lignin-based biopharmaceutical products

Types	Matrix and processing method	Application	Main findings	Ref.
Hydrogel	Doxorubicin was conjugated on lignin–folic acid derived CDs *via* EDC-NHS reaction and loaded with PEGMA, PAA, and ZcPC-based hydrogels	Chemo-phototherapy of breast cancer	Lignin-derived photochemo-hydrogel showing synergistic effect for treatment of breast cancer	41
Cryogel	The cryogel was prepared by mixing lignin and gelatin using the orbital shaking method	Antibacterial, antioxidant, and intravenous delivery	The developed lignin-derived gelatin cryogel showed 7 times higher activity than the pure gelatin cryogel	78
Aerogel	CNF/lignin-based aerogel was developed by a crosslinking method	Antioxidant, antimicrobial, and sustained release properties	The CNF/lignin-based aerogel showed potent antimicrobial activity of tetracycline as well as sustained release properties	83
Oleogel	Lignin castor oil-based oleogel was prepared using a facile synthetic method that employed two saline coupling reagents	Antioxidation	The synthesized oleogel showed good oxidation properties when modified with 20 wt% of lignin	87
Sunscreen	Flavonoids containing lignin sunscreen using the coextraction method	Antioxidant and UV protectant	Musa basjoo and Moso bamboo leaves were used to extract flavonoid-containing lignin using L-cysteine (L-cys)-mediated extraction. Utilizing non-dewaxed sources might boost the flavonoid content of lignin	154
Ointment	Lignin-*graft*-polyoxazoline conjugated triazole: a novel anti-infective ointment	Antimicrobial and antibiofilm	*In vivo* tests of this innovative lignin-based hydrogel have demonstrated its potential as an anti-inflammatory dressing material, to promote healing, and to prevent infection of burn wounds	95
Emulsion	Lignin was dissolved in acetone/water, and then the cosolvent was added to MilliQ water	Drug vehicle and microencapsulation	LNPs prepared were shown to be a highly efficient stabilizer for oil-in-water pickering emulsions	155
Suspensions	The synthesis of lignin aqueous hydrotropic solution by a greener and facile method	Drug delivery	The synthesized LNP solution has potential for the delivery of drugs and bioactive compounds in biomedical applications	129
Nanoformulations	Synthesized nano and microparticles using a green synthetic method	Antioxidant	LPs showed good antioxidant activity against *E. coli* and *Salmonella enterica*, reducing the intracellular ROS level	156
CNTs	Developed nitrogen-doped lignin-derived carbon nanotubes by the pyrolysis method	Drug delivery	High photothermal conversion efficiency of 58.8% was obtained	157
Carbon dots	Lignin-based CQDs were prepared using a hydrothermal method	Bioimaging	L-CQDs exhibited low cytotoxicity and good cellular biocompatibility, demonstrating significant potential for bioimaging applications	143
Biomedical devices	GOx–SiO_2/Lig system was integrated with single-walled carbon nanotubes and platinum nanoparticles	Biosensors for medical and bacterial sensing	The glucose biosensor presented a high sensitivity of 0.78 μA mM^{-1}. The linear response range of 0.5–9 mM has a detection limit (LOD) of 145 μM	158
Biopolymer matrix	Lignin blended with different biopolymeric blends like starch, polylactic acids, polyhydroxybutyrate, and polyamides	Tissue engineering & regenerative medicine, and therapeutic delivery systems	Biodegradability, strong mechanical reinforcement ability, unique structural properties, renewability, and diverse possible modifications of its unique chemical structure	159

more resistant to UV light, and even more eco-friendly since they improve biodegradability.[23]

Lignin-based nanoparticles present another mechanistically interesting system due to the amphiphilic nature of lignin, which can self-assemble into these well-ordered tiny core–shell structures. This allows it to act as both the carrier and the protective shell for bioactive molecules.[24] These reflect the reactivity and capacity for crosslinking and interfacial properties important in inducing biocompatibility and surface interactions. The source of the lignin and its purity are other significant factors affecting performance. Native lignin and organosolv lignin are usually more uniform and reactive than technical Kraft or soda lignin, which contain some sulfur and heterogeneous linkages, which limit their potential biomedical utility.

The mechanistic aspects of lignin-based formulations are summarized in terms of their physical state, functional role, and key chemical groups (Table 4). These features determine their main biomedical applications, along with the advantages and limitations influencing their overall performance. In summary, this comparative analysis gives further evidence of the adaptability of lignin as a multifunctional component biomaterial and defines some of the structural features that lead to the variations in performance in relation to the diverse biomedical applications.[23,24,165]

Despite these advances, the majority of reports are from the laboratory scale, and further work is required to help translate lignin materials to clinical (or commercial) applications in biomedicine. This requires robust purification, reproducibility studies, and safety evaluations. Continued mechanistic insight is thus necessary, alongside controlled lignin extraction and functionalization, to fully unlock the biomedical avenues for this abundant natural polymer.

4. Frontiers of lignin-based biopharmaceutical development

Lignin, a naturally abundant and renewable biopolymer, holds immense potential in the field of biopharmaceuticals due to its unique structural properties. Recent advancements in lignin functionalization and nanotechnology have opened new avenues for its application in biopharmaceuticals. Despite its shortcomings, due to the wide range of applications, such as in pharmaceutics, cosmetics, and agricultural industries, it is anticipated that lignin will be crucial to future innovations. In biopharmaceutical systems, lignin is predominantly employed as a functional, non-active component, where it serves as a carrier, stabilizing matrix, or performance-enhancing excipient rather than as a standalone therapeutic agent.

Current research demonstrates that lignin contributes to therapeutic outcomes by improving drug stability, encapsulation efficiency, controlled release, and targeting performance, particularly in advanced drug delivery systems. The increasing interest in lignin-based biomedical applications is due to high stability, pH-responsive behaviour, and high encapsulation efficiency.[100] Accordingly, this section discusses established applications of lignin in drug delivery, biomedical platforms, combination strategies, and bioactive lignin-derived compounds, while also highlighting emerging directions and future opportunities in lignin-based biopharmaceutical development.

4.1 Drug delivery system

In pharmaceutical systems, lignin biomaterials have been utilized extensively to develop stimuli-responsive drug delivery systems, and substantial research will be required to completely understand lignin's potential. Moreno *et al.* reported thermo-responsive lignin-based materials incorporated with a low critical solution temperature (LCST). Below the LCST, the lignin-based polymer chain starts existing as random coils due to hydrogen bond interactions. The phase separation occurs due to the difference between temperatures above and below the LCST, resulting in the controlled drug release in the specific area.[166] Similarly, Dinari *et al.* assessed the dual response of a lignin-based nano gel for curcumin loading and release. The nano gel

Table 4 Mechanistic aspects by listing broad categories of lignin-based formulations

Formulation type	Physical state	Role of lignin	Functional groups	Applications	Advantages	Limitations/challenges
Hydrogels	Semi-solid	Crosslinker, antioxidant, antimicrobial agent	Phenolic –OH, COOH	Wound dressings, tissue scaffolds	Biocompatibility, antioxidant protection	Mechanical weakness, limited tunability
Polyurethanes	Solid/elastic	Chain extender, UV stabilizer, filler	Aliphatic –OH, aromatic rings	Soft biomaterials, coatings	Improved strength, UV resistance	Variability in reactivity across lignin types
CNT/lignin composites	Solid/conductive	Dispersant, electron mediator, mechanical enhancer	Phenolic –OH, aromatic rings	Biosensors, conductive scaffolds	Enhanced dispersion, redox activity	Processing complexity
Nanoparticles	Colloidal/liquid	Carrier, stabilizer, active agent	Phenolic –OH, COOH, methoxy	Drug delivery, antioxidant nanocarriers	High surface reactivity, biodegradability	Scale-up, stability in physiological media
Films/coatings	Solid	UV barrier, antimicrobial layer	Aromatic rings, phenolic –OH	Biomedical packaging, wound coatings	Antimicrobial and antioxidant protection	Brittleness, uneven morphology

named lignin-*g*-P(NIPAM-*co*-DMAEMA) was studied for its biodegradability and stimuli-response, overcoming its limitations and enhancing its other properties.[167] Due to lignin's amphiphilic nature, both hydrophilic and hydrophobic drugs can be encapsulated, which can help to protect the encapsulated drugs and also help in their controlled release.[168] Amphiphilic lignin acts as a micelle due to the availability of both hydrophobic and hydrophilic parts. The hydrophobic part generally consists of a phenyl propane skeleton, and the hydrophilic groups consist of phenolic hydroxyl and carboxyl groups.[169] A Π–Π conjugated effect was observed between benzene rings which allowed lignin-based micelles to transport hydrophobic drugs and nutrients through the formation of lignin nano-micelles, which have proven to enhance molecular drug delivery because they exhibit a low critical micelle concentration.[170]

Another area in which lignin is expected to play an important role is targeted drug delivery, particularly for anticancer therapeutics, where lignin-based systems have been widely explored as carriers to enhance drug stability, targeting efficiency, and therapeutic performance. Liu *et al.* developed lignin-based targeted polymeric nanoparticles for efficient and targeted drug delivery of anticancer drug hydroxyl camptothecin (HCPT) *via* folic acid–polyethylene glycol–alkaline lignin conjugates (FAPEG-AL).[128] The high drug loading efficiency, robust stability, moderate particle size, and efficient delivery capacity of FA-PEG-AL/HCPT NPs enhanced the properties and effectiveness of HCPT. In this context, it also enhances blood circulation time and cellular uptake. Another application that can be further explored in the field of drug delivery is incorporating lignin with some already available pharmaceutical drugs to enhance their therapeutic properties. For example, Pishnamazi *et al.* modified lignin to form carboxylated lignin and then studied the pH-dependent release behaviours of carboxylated lignin and its effects on releasing a drug.[146] The drug that was incorporated with carboxylated lignin was paracetamol, a standard antipyretic and analgesic prescribed by doctors worldwide. The results were quite optimistic and illustrated an increase in the rate of release of paracetamol when incorporated with carboxylated lignin. This can be explained by the lower degree of interaction between lignin and the API due to the deprotonation of the –COOH group. Recently, lignin has also been incorporated into the formulation for the SNEDDS (solid self-nanoemulsifying drug delivery system) as a surfactant, as reported by Dai *et al.*, in which a lignin-based surfactant in the SNEDDS was prepared to improve the stability, absorption, and effectiveness of *trans*-RSV.[171]

These findings collectively highlight the versatility of lignin as a functional component in advanced drug delivery systems, capable of influencing both targeting efficiency and release behaviour. In drug delivery applications, the specific location of lignin and the binding mode within the gel matrix critically impact drug loading, diffusion, and release performance. Structures where lignin is covalently attached are inclined to display slower, diffusion-controlled release, while physically incorporated lignin frequently aids rapid and responsive release profiles. Thus, lignin should be regarded not only as a universal matrix polymer, but also as a multifunctional additive whose contribution to mechanical, chemical, or biological properties depends on its integration strategy and chemical structure.

4.2 Biomedical applications

Biomedical application is the application of technology and engineering in life sciences, especially related to materials with therapeutic or medicinal properties.[172] Biomedical applications have a wide range of applications in medicine, including diagnostic imaging technologies such as MRI, CT scans, and other novel research areas of genetic engineering, gene therapy, and biosensors. Jedrzak *et al.* developed an enzyme-based biosensor with the help of a functional biohybrid silica–lignin, which was used to immobilize glucose oxidase on its surface for glucose sensing.[158] The synthesized biosensor has high sensitivity and a linear response range of 0.5–9 mM and has a detection limit (LOD) of 145 μM.

Lignin will have substantial applications in tissue engineering soon due to its emerging nature and diverse applications. Lignin-based nanomaterials are developed into nanofibers and hydrogels, which are fabricated to mimic the extracellular matrix and promote tissue growth and regeneration.[173] Subsequently, the porous structure helps us to influence the geometry, density, surface areas, and permeability, which makes it suitable for different medical uses as its pores can be used to lighten weight in bone tissue engineering applications, and also apply its absorption ability that can be used to control the drug loading and release activity.[43]

Lignin's application in wound healing has only reached a surface level so far, and there is still much to be done; however, the results reported to date have been fruitful. For instance, Ravishankar *et al.* reported a hydrogel of chitosan–alkali lignin, which was synthesized using cross-linkages, and no toxicity was observed in either *in vitro* or *in vivo* studies.[73] Lignin can also help regulate bone metabolism due to its ability to scavenge ROS, which will help restore the uncoupling bone remodelling and prevent and cure many orthopaedic diseases.[174]

4.3 Combination therapy

Combination therapy refers to the use of two or more therapeutic agents or treatment modalities together to achieve enhanced or synergistic effects. It has become a cornerstone in many biomedical applications, and numerous compounds are being evaluated and explored for their synergistic potential and enhanced therapeutic efficacy. Combinational therapy is of great value due to certain reasons, like fewer side effects, environmentally friendly drug synthesis, and enhanced drug efficacy with a material possessing the same properties or another therapeutic property. Siddiqui *et al.* reported a novel 4-in-1 strategy on

how to combat colon cancer, in which the first strategy involves the action of a chemotherapeutic drug on cancer cells. Secondly, antioxidants present in lignin and quercetin act on cells under high oxidative stress to prevent cancer relapse. Subsequently, quercetin modulates to overcome drug efflux. Lastly, hyaluronic acid acts as a ligand to target lignin nanoparticles to cancer cells through CD44 receptors.[175] Combination strategies in cancer research often aim to enhance therapeutic efficacy through synergistic mechanisms. In this context, Pylypchuk *et al.* synthesized lignin nanoparticles from eucalyptus and spruce wood lignin.[176] These nanoparticles show anticancer properties against hepatocellular carcinoma (HCC). There was also high dose dependency in both cases, although E-LNPs more efficiently inhibited the growth of aggressive HCC cells than less polar S-LNPs. Importantly, the study revealed a direct correlation between lignin surface chemistry and anticancer activity, where a higher number of carbohydrate subunits on the lignin nanoparticle surface was associated with enhanced biological activity.

Synergistic combination is another area where lignin's potential could be unleashed. Liu *et al.* reported using lignin and quercetin as a natural, effective, and cheap antioxidant.[177] The free radical scavenging ability was even better than that of pure quercetin, which could be explained by the encapsulation of quercetin into lignin that preserved its antioxidant properties under UV radiation for a longer time. Another research conducted by Figueiredo *et al.* explained the effectiveness of biodegradable lignin-based nanoparticles in pharmaceutical sciences.[130] Three different kinds of nanoparticles were made, including Fe_3O_4-LNPs, LNPs, and pLNPs. The efficacy of loading poorly water-soluble drugs was evaluated, leading to improved release profiles, and the antiproliferative effect was enhanced. With the increase in their surface structure, LNPs were modified to target moieties to increase the cellular interaction with cancer cells, which can be useful for cancer therapy.

4.4 Bioactive compounds from lignin

Bioactive compounds are the naturally occurring compounds found in plants, animals, and microorganisms that have a positive impact on human health. There is a long list of compounds that fall under the category of bioactive compounds, which includes flavonoids, antioxidants, terpenes, alkaloids, probiotics, prebiotics, and many more. Bioactive compounds found in vegetables and fruits possess the potential to prevent certain chronic conditions, such as cancer, cardiac diseases, and diabetes.[178] Lignin, being rich in polyphenols, is an immense source of bioactive compounds, which are responsible for its therapeutic behaviour.[179] If such bioactive compounds are efficiently extracted from lignin, they can be useful in multiple therapeutic applications.

The presence of polyphenolic bioactive compounds imparts high antioxidant properties in lignin, which makes it a suitable material for use in cosmetics and pharmaceuticals. Vinardell *et al.* examined the antioxidant properties of lignin extracted from different sources, such as LS, bagasse, steam explosion, and curan.[180] The results confirmed that lignin obtained from all four of these possesses antioxidant properties, with bagasse being the most potent. The extracted lignin from different sources was also tested to check its toxicity to human skin and eyes, which also confirmed that lignin is safe when it is exposed to skin and eyes. Water-soluble lignin generally has better antioxidant properties than traditional lignin due to its low molecular weight.[181] Apart from antioxidant and anticancer properties, lignin also possesses anti-inflammatory properties, but this field has not been explored as much as lignin's application in antioxidant and anticancer drugs. Wang *et al.* worked on two types of water-soluble lignin; one was derived from bamboo (WSL BM) and the other from the wheat stalk (WSL-WS).[181] Anti-inflammatory properties were tested when some mice were given the treatment for colitis, and anti-inflammatory effects were observed by regulating key signalling pathways involved in inflammation by activating the Nrf2 pathway and inhibiting NFκB to treat bowel diseases. The neuroprotective effect is the ability of some molecules or substances to protect the neurons present in the brain and nervous system, and it has become a beacon of hope in the treatment of diseases like Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis (ALS). Lignin applications have started to creep into the area of neuroprotective effects; however, this area is new, and further studies need to be done to evaluate its full potential. For instance, Ito *et al.* converted lignin into its bioactive lignophenol derivative.[182] It was found that a modified lignocresol derivative from bamboo protected SH-SY5Y cells from H_2O_2-induced apoptosis and had neuroprotective effects against oxidative stress, OGD stress, tunicamycin stress, PSI stress, and retinal damage, which eventually suggests that it could have application in treating several neurodegenerative diseases.

5. Challenges and future prospects

Lignin, despite its wide range of applications and promising developments, still has several challenges that hinder its clinical and industrial translation. Here, key issues including structural heterogeneity, lack of standardization in extraction and characterization methods, and limited understanding of its biological interactions were discussed. Additionally, regulatory uncertainties and scalability concerns pose further obstacles. Addressing these limitations through interdisciplinary research, advanced processing techniques, and policy frameworks will be crucial for unlocking lignin's full potential in biomedical applications.

5.1 Structural heterogeneity and standardization

Standardization of lignin may be the most significant problem related to lignin because the chemical structure and molecular properties of lignin are still uncertain, as they

change every time with the change in the method of extraction.[183,184] The structure and chemical composition of lignin also depend upon the source or species of the plant that is being used to extract lignin.[185] The primary goal of scaling up lignin processing is its valorization into value-added materials or products. However, achieving cost competitiveness in industrial-scale biorefinery plants remains challenging, particularly in the lignin isolation step, as lignin is a by-product of the extraction process rather than the primary target.[186] Some of the methods to extract lignin are detrimental to the environment due to the use of high temperatures and pressures, along with the use of harsh chemicals. To combat these existential issues, the extraction of lignin *via* biorefineries is a good alternative that revolves around minimizing the extent of alternative energy and maximizing the efficacy of the lignin that is extracted.[187] Similarly, deep eutectic solvents (DESs) are another way to extract lignin in a green and sustainable way by increasing the reactivity of lignin, which makes its functional group more accessible.[187]

Isolation of lignin, its transformation, and minimization of structural changes, as well as keeping the extraction procedure low-cost, are big challenges.[188] Lignin degradation is a multistep process that involves various reactions and also produces large amounts of side products.[189] There's a need to use potent oxidation agents to help the enzymes attack any lignin site that was found to be accessible, but this could also lead to dehydrogenation, which could lead to oxidation coupling *via* phenolic moieties.[190] The heterogeneity of lignin results in the heterogeneity of aromatic compounds, which is another problem. However, a new approach called biological funnelling is being used in which some microbes are used to convert aromatic molecules into intermediates, which are funnelled into the central carbon atom.[191] Lignin degradation poses another problem that we need to tackle before we can start utilizing lignin at its full potential.

5.2 Translational hurdles in lignin biopharmaceutical development

Biocompatibility. In the case of lignin, the problem arises when it is used as a biomaterial at a nano-scale, as the properties of materials change when they are taken into such a small scale. Nanoparticles have a high propensity to infiltrate biological membranes and cells with ease, which can lead to their accumulation in cells, tissues, and blood, and can have a deleterious effect on human health. Nanoformulations also act as catalysts to increase the rate of reaction of reactive oxygen species (ROS) that can lead to oxidative stress, which may eventually lead to lipid peroxidation and mitochondrial and DNA damage, resulting in cell death.[192] Lignin, being a low-toxicity natural polymer, also possesses ROS-scavenging properties that aid in further biological applications. Organosolv and soda exhibit better cellular compatibility and low toxicity. LS also showed water solubility, good hemocompatibility, and sufficient cytotoxicity. Meanwhile, KL exerted biocompatibility owing to sulfur impurities. These occur due to oxidative stress and glutathione (GSH) depletion induced by the lignin's polyphenolic functional groups.[193]

Immunogenicity. Generally, purified lignin is considered highly biocompatible, featuring very low immunogenicity; it is more often characterized by anti-inflammatory, antioxidant, and soothing properties rather than the ability to provoke an immune response. It is a common misconception that lignin is an allergen, while allergic reactions to wood dust in general are typically caused by other volatile "extractive" chemicals, such as quinones and terpenes, rather than by the structural lignin itself. However, the biological properties of lignin are strongly dependent on its source and the extraction method used. While purified LNPs demonstrate high biocompatibility in preclinical studies, industrial-grade technical lignin, such as KL, can work as a mild skin sensitizer owing to residual processing chemicals. Also, some particular types of lignin–carbohydrate complexes demonstrate an immunomodulatory capability, *i.e.*, softly stimulating the innate immune system, and this property is under study as a candidate for vaccine adjuvants, which is different from a harmful immunogenic reaction. Research on lignin for internal application in humans, such as drug delivery, remains preclinical; thus, human clinical data about the immunogenicity of lignin are missing.[194–197]

Sterilization and endotoxin control. The effective sterilization of lignin materials is challenging because methods such as gamma irradiation, ethylene oxide treatment, or sterile filtration can alter the molecular weight and surface chemistry. These changes may compromise performance and reproducibility. Additionally, as a botanical and compositionally variable polymer, lignin poses challenges in maintaining endotoxin and impurity levels within pharmacopeial limits. The absence of harmonized purification standards and validated Chemistry, Manufacturing, and Controls (CMC) procedures remains a critical obstacle to regulatory acceptance.[196]

Pharmacokinetics and pharmacodynamics. To date, no human trials have evaluated lignin-based formulations. Available studies remain preclinical, concentrating on nanoparticle synthesis and *in vitro* assays. A specific pharmacokinetic (PK) or pharmacodynamic (PD) model for lignin carriers has not yet been developed. Although other nanocarrier systems often increase drug bioavailability and reduce clearance relative to free drugs, comparable ADME data for lignin nanoparticles are absent.[198] Developing quantitative PK/PD models will be crucial for predicting human exposure and establishing safe and effective dosing strategies.

Photothermal and oxidative-stress considerations. Lignin-derived carbon nanotubes (CNTs) and carbon quantum dots (CQDs) exhibit useful photothermal and photocatalytic properties for cancer therapy and antimicrobial applications. Their efficiency not only depends on the nanostructure and surface chemistry, but can also lead to the formation of

reactive oxygen species (ROS) under illumination, disrupting cellular homeostasis and provoking oxidative stress.[199] Because lignin is inherently antioxidant, surface coating may attenuate these effects and improve compatibility. Even so, comprehensive *in vivo* analyses of oxidative balance, biodistribution, and long-term toxicity are still lacking.[200]

Despite growing academic interest, lignin remains a preclinical biomaterial. The absence of validated PK/PD data, standardized biocompatibility testing, reliable sterilization and endotoxin control, and reproducible CMC documentation continues to impede translation. Bridging this gap will require coordinated studies that integrate pharmacological testing, regulatory-grade material characterization, and long-term toxicology in line with ICH, ISO, and FDA/EMA expectations before lignin can progress toward clinical evaluation.

5.3 Toxicity mechanisms and long-term biodegradation of CNTs and quantum dots

Direct evidence linking the long-term toxicity, persistence, or metabolic fate of carbon nanotubes (CNTs) and carbon quantum dots (CQDs) remains limited; however, multiple studies indicate characteristic biological responses that warrant attention. CNTs can exert cytotoxic or inflammatory effects in cells and animals through mechanical injury, oxidative stress, and interference with intracellular pathways. Their surfaces promote the generation of reactive oxygen species (ROS), which in turn deplete glutathione (GSH) and disrupt the redox balance, ultimately leading to mitochondrial damage and cell death.[193,200] The extent of these effects depends on the tube length, surface functionalization, and the degree of aggregation.

The breakdown of CNTs proceeds either by chemical oxidation or biological transformation. Enzymatic routes, particularly those involving peroxidases such as myeloperoxidase (MPO), horseradish peroxidase (HRP), and lactoperoxidase (LPO), have been extensively examined. HRP was first reported to oxidize single-walled CNTs, but later work showed that much of this activity originates from a Fenton-type reaction driven by iron released when the enzyme's heme group decomposes in the presence of hydrogen peroxide.[199,201–203] The resulting hydroxyl radicals (·OH) attack the graphitic lattice, producing fragmented and oxygenated structures. Reported degradation rates vary from a few days to several decades, illustrating the strong dependence of the process on reaction conditions.[204]

Microbial activity can also modify CNTs. Bacteria such as *Labrys* sp., *Shewanella*, and *Burkholderia* species generate H_2O_2 and Fe(II) simultaneously, enabling biogenic Fenton-like oxidation of CNTs.[205,206] This pathway converts resistant carbon frameworks into smaller, oxidized fragments, although complete mineralization is a slow process and may require months under favorable conditions. The persistence of CNTs in soils and aquatic systems, consequently, remains a realistic concern.

Morphologically, some needle-like multiwalled CNTs resemble asbestos fibers, raising the possibility of similar pathogenic outcomes. Experimental inhalation studies have linked such materials to pleural fibrosis, mesothelioma, and chronic pulmonary inflammation.[207,208] Besides human health, CNTs also affect plants and microorganisms: growth inhibition, reduced germination, and membrane disruption have all been documented.[209,210] As production and use increase, environmental accumulation and ecotoxicological exposure will require systematic risk evaluation.

In contrast, lignin-functionalized CNTs and CQDs appear less harmful. The lignin coating supplies antioxidant phenolic groups that can quench ROS and limit oxidative stress during photothermal activation. Experimental work demonstrates lower cytotoxicity and improved cellular tolerance for lignin-coated nanostructures compared to unmodified carbon analogues.[200] Even so, detailed *in vivo* studies addressing biodistribution, chronic exposure, and degradation kinetics are still missing. Collectively, lignin modification offers a promising route to enhance the biocompatibility and environmental stability of carbon nanomaterials; however, a clear understanding of their long-term fate remains essential for safe biomedical and industrial applications.

5.4 Regulatory hurdles

A specific framework for lignin-based materials does not currently exist, especially for biopharmaceuticals. Rules and regulations are stringent when it comes to medicines, and no traces of toxic materials are generally accepted.[211] Lignin has already shown various biological activities in clinical studies. However, lignin, being a compound or an excipient in formulation, has also been evaluated for metabolism studies. Metabolism studies point out that lignin is primarily undigested in the gastrointestinal tract; the lack of biodegradation permits careful attention. The nano-scale non-digestible lignin-based materials may persist at the intestinal interface and interact with the mucus layer and epithelial surface. The abundant phenolic hydroxyl groups and aromatic groups present in lignin can help adhesion to mucins and epithelial membranes through hydrogen bonding, hydrophobic interactions, and π–π stacking, possibly leading to interfacial accumulation. Such a buildup of undigested lignin raises alarms regarding long-term exposure, increased epithelial permeability, local inflammation, or disruption of gut microbiota equilibrium. Thus, the absence of digestive metabolism highlights the need for targeted studies, such as evaluations of mucus penetration, epithelial retention, and long-term exposure. These drawbacks emphasize the necessity of a lignin-specific regulation framework that considers interfacial persistence and nano-bio interactions rather than relying solely on conventional bulk-material toxicity models.[212]

The use of lignin in the pharmaceutical field has not yet been approved by major regulatory agencies worldwide,

including the Food and Drug Administration (FDA) and the European Medicines Agency (EMA).[24] Apart from that, there are also no certified criteria for engineered nanomaterials, but the FDA and the European Commission are working to design strict regulations regarding the optimum use of nanoparticles.[213,214] For pharmaceutical applications, lignin-derived systems would be expected to comply with the International Council for Harmonisation (ICH) guidelines, particularly Q8 (R2) on Pharmaceutical Development and Q12 on Pharmaceutical Product Lifecycle Management. These frameworks emphasize the definition of Critical Quality Attributes (CQAs), implementation of Quality by Design (QbD) principles, and establishment of a robust Chemistry, Manufacturing, and Controls (CMC) framework to ensure batch reproducibility and product consistency throughout the development lifecycle.[215,216] For biomedical device applications—such as lignin-based wound dressings, hydrogels, or 3D-printed scaffolds—evaluation is guided by the ISO 10993 standards for biological safety and the European Union Medical Device Regulation.[217] Depending on the degree of invasiveness and intended use, such products are generally categorized as class IIb or class III, requiring a comprehensive biological evaluation that encompasses cytotoxicity, sensitization, systemic toxicity, implantation, and degradation analyses.[218]

Thus, most pharmaceutical companies will be in a dilemma to give lignin a chance, as it will be time-consuming and also require a lot of capital without knowing whether it will ever be approved or not. Safety and efficacy standards should be met to come on par with the pharmaceutical regulations that are set for other biomaterials. General protocols of testing should be followed, having a global vision in mind to meet the demands of the whole of mankind. We still have a lot to explore about lignin's properties and its toxicity, molecular behaviour at different sizes, and how it will affect its medicinal and therapeutic properties. Addressing these aspects will be essential for transforming lignin from a promising experimental biomaterial into a clinically viable and regulatory-compliant therapeutic platform.

5.5 Integration with existing pharmaceutical processes

Integration of biomaterials with existing pharmaceutical processes has also been on the rise to increase the therapeutic properties of existing drugs and minimize the side effects. The biomaterial, which is generally incorporated with the drug, is known as an active pharmaceutical ingredient (API). Lignin can be used as a modifier to enhance the bioavailability of APIs because of its amorphous nature, which often results in higher free energy.[219] The problem with APIs, in general, is that many pharmaceutical companies are always looking for faster and more economical methods to produce APIs without any thought of the safety or rules and regulations.[220] This is detrimental to both human health and the environment if a company uses hazardous chemicals just for the sake of making a profit. For instance, a big pharmaceutical corporation can make lignin-based APIs without following safety and regulation guidelines, as there are no specific guidelines for lignin biomaterials. Pishnamazi *et al.* reported one example where lignin was integrated into existing pharmaceutics (acetylsalicylic acid tablets), where organosolv lignin, along with microcrystalline cellulose (MCC) and lactose, was added to aspirin, resulting in increased hardness and release rate of aspirin.[145]

Lignin-based biopharmaceuticals have a great deal of potential to advance biomedical applications, combination treatments, drug delivery methods, and the extraction of bioactive components. It is essential to standardize lignin sources and quality, taking into account extraction techniques, quality control, and source variability. One must overcome regulatory barriers, such as the absence of certain laws, safety requirements, and international harmonization. Also, the incorporation of lignin into current pharmaceutical processes demands that compatibility, processing difficulties, scale-up issues, interactions with other components, and cost implications should be carefully considered. Regardless of these challenges, addressing them all at once will pave the way for the successful integration of lignin into the biopharmaceutical sectors, offering creative and long-lasting remedies for medical demands in the future.

5.6 Comparative context with existing biomaterials

The widely used biopolymers, such as hyaluronic acid and collagen, which are often expensive and sourced from animal tissues, are compared to lignin, an agri-residue-based biopolymer, which offers high cost and supply advantages. In contrast to alginate and collagen hydrogels, which primarily provide structural support, lignin inherently exhibits antioxidant and antimicrobial activities due to its phenolic and aromatic domains.[221–223] Additionally, the molecular structure of lignin allows extensive chemical modification, enabling the tuning of stiffness, degradation rate, and surface interaction features that are comparatively more limited in natural polymers with fixed backbone chemistries.[224] However, the enzymatic biodegradation of lignin is slower than that of polysaccharide-based hydrogels; this property can be advantageous for applications requiring prolonged material stability or sustained release. Collectively, these factors position lignin as a functionally competitive and economically scalable biomaterial candidate.[225,226]

6. Conclusion

Lignin, a sustainable biopolymer, has shown significant potential in the development of various biopharmaceutical formulations due to its structural diversity and inherent biological activities. Its antioxidant, antimicrobial, and anti-inflammatory properties, along with biocompatibility and availability, make it a strong candidate for use in pharmaceutical and biomedical applications. In this review,

we have explored a wide range of lignin-based formulations, including semisolid systems such as hydrogels and cryogels, liquid forms like suspensions and emulsions, and solid platforms like nanoparticles, nanocomposites, and biomedical devices. These materials offer innovative solutions for drug delivery, wound healing, and other therapeutic strategies, often enhancing performance while also contributing to sustainability. However, its use is still limited by variability in composition, extraction methods, and the lack of standardized purification and testing protocols. Most studies remain at the laboratory scale, and systematic data on long-term safety, pharmacokinetics, and biodegradation are still missing. For lignin to move closer to real pharmaceutical use, greater attention is needed to ensure batch uniformity, reproducibility, and regulatory compliance. Overall, lignin represents a sustainable and promising platform for future healthcare materials. Continued collaboration between materials science, pharmacology, and regulatory research will be key to turning this potential into safe, effective, and commercially viable biopharmaceutical products.

Abbreviations

AIDS	Acquired immune deficiency syndrome
ALS	Amyotrophic lateral sclerosis
API	Active pharmaceutical ingredient
ATRP	Atom transfer radical polymerization
BB	Blemish balm
BM	Bamboo
CDs	Carbon dots
CNTs	Lignin-based carbon nanotubes
DMI	Dimethyl isosorbide
DESs	Deep eutectic solvents
E. coli	*Escherichia coli*
ECH	Epichlorohydrin
EMA	European Medicines Agency
FA-PEG-AL	Folic acid–polyethylene glycol–alkaline lignin conjugates
FAPEG-AL	Folic acid–polyethylene glycol–alkaline lignin conjugates
FDA	Food and Drug Administration
Fe_3O_4-LNPs	Fe_3O_4-infused lignin nanoparticles
HCC	Hepatocellular carcinoma
HCPT	Hydroxyl camptothecin
HIV-1	Herpes simplex virus type 1
HSEs	Human skin equivalents
HSV-2	Herpes simplex virus type 2
KL	Kraft lignin
KL-PEG	Kraft lignin–polyethylene glycol conjugate
K-cLNPs	Kraft-colloidal lignin nanoparticles
LCST	Low critical solution temperature
LNCs	Lignin nanocapsules
LNPs	Lignin nanoparticles
LS	Lignosulfonates
MCC	Microcrystalline cellulose
Mt	Montmorillonite
NEBA	*N*,*N*′-Ethylenebisacrylamide
NIPAM-*co*-DMAEMA	Nanogel named lignin-*g*-P
NMBA	*N*,*N*′-Methylenebisacrylamide
OMt	Organo-montmorillonite
PCL	Polycaprolactone
PEG	Poly(ethylene glycol)
PEGDGE	Poly(ethylene glycol) diglycidyl ether
PHB	Polyhydroxybutyrate
PLA	Polylactic acid
PMVE/MA	Poly(methyl vinyl ether-*co*-maleic acid)
PU	Polyurethane
PVA	Polyvinyl alcohol
RAFT	Reversible addition–fragmentation transfer
ROS	Reactive oxygen species
S. aureus	*Staphylococcus aureus*
SNEDDS	Solid self-nanoemulsifying drug delivery system
SPF	Sun protection factor
WS	Wheat stalk
WSL	Water-soluble lignin

Author contributions

Kshitij Rawat: conceptualization, visualization, investigation, validation, writing original draft – review & editing; Ravneet Kaur: investigation, validation, writing original draft – review & editing; Anil Kumar Pujari: investigation, validation, writing original draft – review & editing; Kunal Gogde: investigation, validation, writing original draft – review & editing; Devesh Mohne: investigation, validation, writing original draft – review & editing; Seema Kirar: validation, review & editing; Yeddula Nikhileshwar Reddy: validation, review & editing; Pooja Ramji Yadav: validation, review & editing; Prakash Y. Khandave: validation, review & editing; Abhay H. Pande: fund acquisition, validation, review & editing; Jayeeta Bhaumik: conceptualization, visualization, fund acquisition, supervision, validation, review & editing.

Conflicts of interest

There are no conflicts to declare.

Data availability

No primary research results, software, or code have been included, and no new data were generated or analysed as part of this review.

Acknowledgements

All the authors are thankful to the BRIC NABI, the Department of Biotechnology (DBT), Government of India (GOI), for providing funding, infrastructural support, and instrumental facilities. The authors thank the Department of Biotechnology for funding the lignin valorization project

(Grant No. BT/PR42965/PBD/26/821/2021). K. R. appreciates the University Grants Commission (UGC) for the senior research fellowship. P. R. Y. is grateful to the Indian Council of Medical Research (ICMR) for the junior research fellowship. S. K. thanks the Department of Science and Technology (DST) for the fellowship under the WOSA scheme. The authors thank Prof. Deepa Ghosh, Scientist G, INST Mohali, for her insightful comments.

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