

Lignin-Derived and Associated Polyphenolic Compounds in Woody Plants: Structural Elucidation, Synthetic Pathways, Characterization Techniques, and Industrial Bioactivities

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Abstract

Lignin is the second most abundant natural biopolymer on Earth, functioning as a primary structural matrix in the secondary cell walls of woody plants. Composed of complex, cross-linked, hydroxylated, and methoxylated phenylpropanoid units, lignin and its associated polyphenols possess unique structural flexibility, UV-shielding, radical scavenging, and antimicrobial properties. Historically managed as a low-value byproduct of the pulp and paper industry, recent biorefinery innovations have repositioned lignin as a crucial sustainable precursor for high-value biomaterials, green composite fillers, and targeted biomedical carriers. This review provides a rigorous, critical synthesis of lignin chemistry, detailing monolignol biosyntheses (p-coumaryl, coniferyl, and sinapyl alcohols), radical coupling polymerization mechanisms, and taxonomic variations across gymnosperm softwoods, angiosperm hardwoods, and woody bamboos. Modern structural characterization methodologies including 2D 1H-13C HSQC NMR, 31P NMR, Py-GC/MS, SEC/GPC, and FTICR-MS are comprehensively evaluated alongside commercial extraction protocols (kraft, organosolv, liginosulfonate, and soda processes). Furthermore, quantitative performance metrics across antioxidant (DPPH IC50), UV-blocking (SPF values), antimicrobial (MIC), and drug-delivery (encapsulation efficiency) domains are critically synthesized. Technical limitations regarding structural heterogeneity, condensation reactions, sulfur contamination, commercial scalability, life cycle assessments (LCA), and regulatory hurdles for biomedical translation are thoroughly examined. This work establishes an integrated framework bridging taxonomic lignin chemistry with industrial valorization and sustainable bioeconomy strategy.

Keywords: Lignin valorization; Technical lignins; Structural elucidation; 2D HSQC NMR; Phenylpropanoid biosynthesis; Quantitative bioactivities; Biorefinery scalability.

1. Introduction

Lignin is an intricate, highly branched aromatic macromolecule that accounts for approximately 15% to 35% of the dry lignocellulosic biomass in vascular plants, serving as an indispensable structural support matrix alongside cellulose and hemicellulose.^[1,2] Deposited predominantly during secondary cell wall formation, lignin imparts essential mechanical strength, rigidity, and stem uprightness, while rendering vascular tissues impermeable to aqueous fluid transport.^[3,4] Furthermore, lignification acts as a robust biochemical defense mechanism against pathogen infection, microbial degradation, and environmental oxidative stresses.^[2,5] From a chemical perspective, lignin represents the most abundant renewable reservoir of natural aromatic structures on Earth, making it a pivotal feedstock for transitioning from fossil-dependent chemical industries to a sustainable bio-based economy.^[6,7] Despite its immense natural abundance-generated in excess of 50 million tons annually as a byproduct of industrial pulp, paper, and emerging biorefinery operations-lignin remains substantially underutilized.^[8,9] Historically, over 95% of industrial technical lignins, particularly kraft lignin and lignosulfonates, have been incinerated on-site as low-value thermal fuel to recover process chemicals and generate operational steam.^[8,10] This practice stems primarily from lignin's inherent structural heterogeneity, high polydispersity, thermal instability, and operational recalcitrance caused by unpredictable radical condensation during chemical pulping.^[7,11] However, driven by modern advancements in analytical characterization, targeted depolymerization, green fractionation, and nanostructural engineering, lignin is rapidly transitioning from an under-valued waste stream to a high-value platform material.^[12,13]

While numerous reviews have broadly examined lignin isolation or specific chemical modifications, several major knowledge gaps persist in the current literature. First, conventional reviews frequently discuss lignin in generic terms without adequately differentiating the distinct structural traits imparted by specific woody plant taxa (e.g., gymnosperm softwoods vs. angiosperm hardwoods vs. woody bamboos).^[2,14] Second, existing literature often provides purely qualitative assertions

regarding lignin bioactivities-such as 'strong antioxidant capacity' or 'excellent antimicrobial action'-without critically synthesizing quantitative benchmarks such as DPPH scavenging IC₅₀ values, UV protection factors (SPF), or minimum inhibitory concentrations (MIC).^[15,16] Third, there is a prominent disconnect between laboratory-scale claims of biomedical efficacy and the practical economic, regulatory, and scalability constraints governing commercial translation.^[13,17] Finally, many reviews fail to integrate recent advances in high-resolution analytical techniques, such as 2D 1H-13C Heteronuclear Single Quantum Coherence Nuclear Magnetic Resonance (HSQC NMR) and Quantitative 31P NMR, with commercial process economics and Life Cycle Assessments (LCA).^[18,19] To address these critical knowledge gaps, this review provides a comprehensive and rigorous synthesis of lignin chemistry, biosynthesis, advanced analytical characterization, and industrial applications, specifically focused on woody plant taxa. By establishing explicit linkages between taxonomic origins, isolation chemistries, quantitative performance metrics, commercial scalability, and environmental sustainability, this work offers an integrated blueprint for researchers and bioprocess engineers seeking to unlock the full economic and biomedical potential of lignin-derived polyphenols.

2. Methodology and PRISMA selection strategy

To ensure methodological rigor, transparency, and comprehensive coverage of recent literature, a systematic literature search was conducted adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines.^[20] Primary literature searches were executed across Web of Science, Scopus, PubMed, and Google Scholar covering publication dates from January 2000 through September 2026. The search strategy utilized combinations of Boolean operators with core keywords: ('lignin' OR 'technical lignin' OR 'lignin nanoparticles') AND ('woody plants' OR 'softwood' OR 'hardwood') AND ('structural elucidation' OR '2D HSQC NMR' OR '31P NMR') AND ('biosynthesis' OR 'monolignols') AND ('antioxidant' OR 'antimicrobial' OR 'drug delivery' OR 'UV-shielding'). Furthermore, specific searches focused on commercial

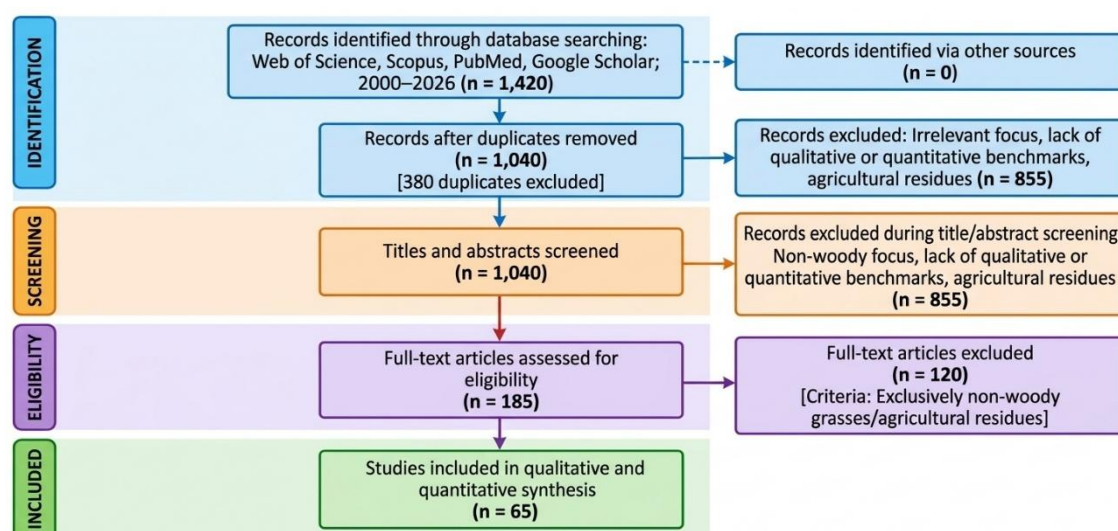


Fig. 1: PRISMA Flow Diagram illustrating literature identification, screening, eligibility, and inclusion process.

processing ('kraft', 'organosolv', 'lignosulfonate', 'soda') and techno-economic evaluation ('life cycle assessment', 'scalability', 'biodegradability'). The primary database search yielded 1,420 records. Following duplicate removal (n = 380), 1,040 titles and abstracts were screened for thematic relevance. Articles were included if they presented primary quantitative data or critical theoretical advancements regarding woody plant lignin biosynthesis, advanced analytical characterization, industrial extraction protocols, or specific bioactivity performance metrics. Studies exclusively focusing on herbaceous agricultural residues or non-woody grasses were excluded unless required for explicit structural comparisons. The focus was on woody taxa based on their dominant share in industrial forestry, higher recalcitrance, unique S/G/H monomeric ratios compared to monocots, and distinct commercial valorization pathways. A total of 185 full-text articles were assessed for eligibility, resulting in 65 highly rigorous primary research articles, authoritative review papers, and technical reports selected for full synthesis within this review (Fig 1).

3. Biosynthetic and polymerization pathways

3.1. General phenylpropanoid enzymatic cascade

Lignin biosynthesis originates within the cytosol via the general phenylpropanoid pathway, utilizing the aromatic amino acid L-phenylalanine (and to a lesser extent L-tyrosine in certain monocots and woody grasses) produced by the shikimate pathway.^[2,21] The initial entry step is catalyzed by Phenylalanine Ammonia-Lyase (PAL), which performs non-oxidative deamination of L-phenylalanine to generate trans-cinnamic acid.^[21,22] Successive hydroxylation and methylation reactions establish the functional aromatic substitution patterns characteristic of monolignol precursors.^[2,23] Trans-cinnamic acid is hydroxylated at the C4 position by Cinnamate 4-Hydroxylase (C4H), a membrane-bound Cytochrome P450 monooxygenase, producing p-coumaric acid.^[22] Activation of p-coumaric acid to p-coumaroyl-CoA is mediated by 4-Coumarate:CoA Ligase (4CL).^[24] The metabolic pathway branches further through downstream enzymes: Hydroxycinnamoyl-CoA Shikimate/Quinate Hydroxycinnamoyl Transferase (HCT) and p-Coumarate 3-Hydroxylase (C3H) catalyze

the conversions leading to caffeoyl-CoA.^[2,24] Caffeoyl-CoA is subsequently O-methylated at the C3 position by Caffeoyl-CoA O-Methyltransferase (CCoAOMT) to yield feruloyl-CoA.^[25] Reduction of these hydroxycinnamoyl-CoA thioesters to their corresponding aldehydes is executed by Cinnamoyl-CoA Reductase (CCR), followed by NADPH-dependent reduction to hydroxycinnamyl alcohols (monolignols) catalyzed by Cinnamyl Alcohol Dehydrogenase (CAD).^[21,26] The synthesis of sinapyl alcohol, the building block for syringyl (S) lignin units, requires Ferulate 5-Hydroxylase (F5H), a specialized Cytochrome P450 enzyme that hydroxylates coniferaldehyde or coniferyl alcohol at the C5 position, followed by O-methylation via Caffeic Acid O-Methyltransferase (COMT).^[2,27] Differential regulation, expression, and substrate specificity of these pathway enzymes directly dictate the proportion of p-coumaryl alcohol (yielding p-hydroxyphenyl, H units), coniferyl alcohol (yielding guaiacyl, G units), and sinapyl alcohol (yielding syringyl, S units) synthesized within plant cells.^[2,28]

3.2. Radical coupling polymerization and combinatorial lignification

Following cytoplasmic synthesis, monolignols are transported across the plasma membrane into the apoplastic cell wall matrix via ABC transporters and passive diffusion mechanisms.^[2,29] In the apoplast, secretable oxidative enzymes-specifically cell wall-bound Class III Peroxidases (utilizing hydrogen peroxide, H₂O₂) and Laccases (utilizing molecular oxygen, O₂)-catalyze the one-electron oxidation of monolignol phenolic hydroxyl groups to form resonance-stabilized phenoxy radicals.^[29,30] Unusually for biological macromolecules, lignification is not a template-driven process; instead, it proceeds via purely chemical, combinatorial radical coupling of these phenoxy radicals.^[6,31] The delocalization of the unpaired electron across the aromatic ring and the conjugated cinnamyl alcohol side chain (at positions O-4, C-1, C-3, C-5, and C-β) permits diverse radical coupling modes.^[6] The primary coupling event typically involves a monolignol radical reacting at its C-β position with an elongated phenolic end-group of a growing polymer, resulting in dominant linkage types such as β-O-4' (aryl ether), β-β' (resinol), β-

Table 1: Comparative structural traits, monolignol proportions, and linkage profiles across major woody plant taxonomic divisions^[2,6,14,33-36]

Taxonomic Group	Representative Species	Monolignol Composition	Dominant Linkages	S/G Ratio	Structural Characteristics
Gymnosperm Softwoods	Pinus taeda, Picea abies, Abies alba	G (>95%), H (<5%)	β-O-4 (45-50%), 5-5 (10-15%), β-5 (9-12%)	N/A (G-dominated)	Highly cross-linked, dense C-C network, elevated recalcitrance
Angiosperm Hardwoods	Populus trichocarpa, Betula pendula	G (30-50%), S (50-70%), H (<2%)	β-O-4 (60-75%), β-β (5-10%), β-5 (3-6%)	1.2 - 3.0	Linear architecture, higher β-O-4 content, lower thermal recalcitrance
Woody Bamboos / Monocots	Bambusa vulgaris, Dendrocalamus strictus	G (40-50%), S (40-50%), H (5-10%)	β-O-4 (50-60%), ester/ether hydroxycinnammates	0.8 - 1.5	Abundant hydroxycinnamic acids (ferulate/coumarate) cross-linking

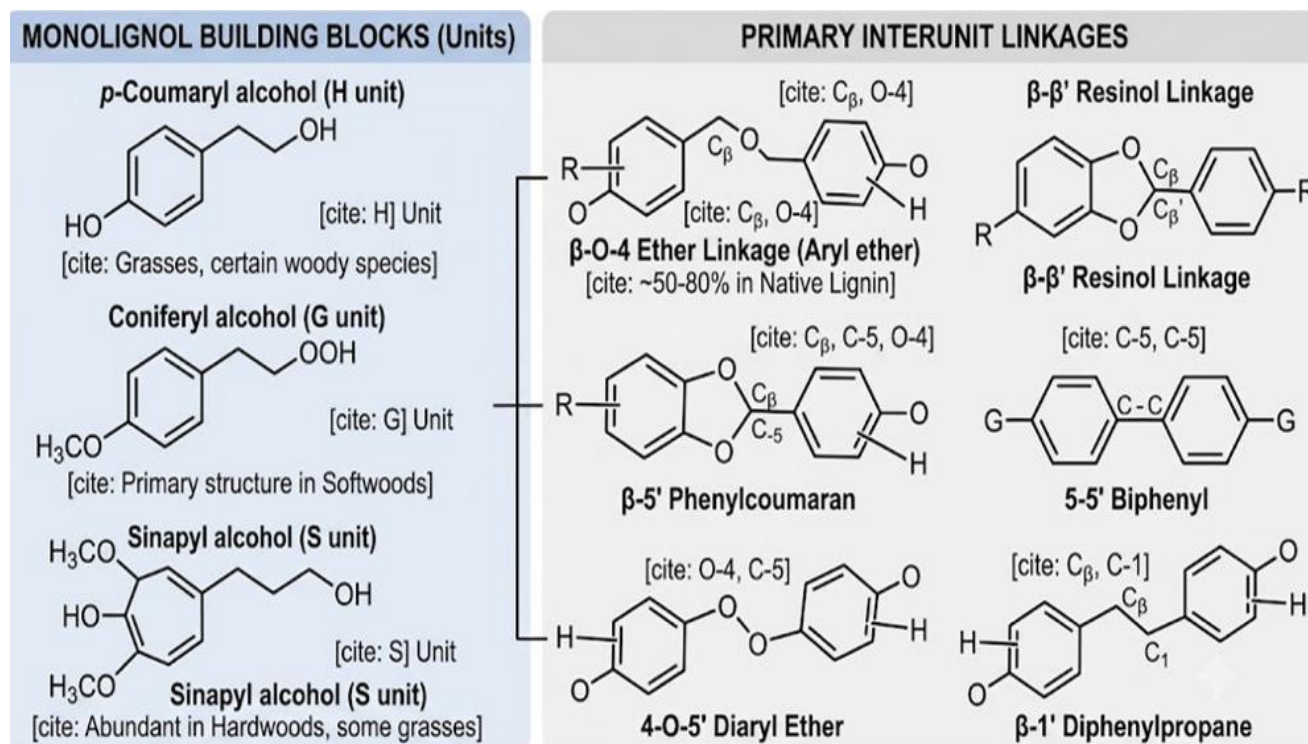


Fig. 2: Molecular structures of fundamental monolignol building blocks and primary interunit linkages.

5' (phenylcoumaran), 5-5' (biphenyl), and 4-O-5' (diaryl ether).^[6,32] This non-deterministic coupling mechanism accounts for the extreme macromolecular heterogeneity, polydispersity, and optical inactivity observed in natural plant lignins.^[6]

4. Taxonomic diversity and structural characteristics

4.1. Structural classification across woody taxa

Lignin composition varies systematically across major taxonomic divisions of woody plants, driven by evolutionary adaptations in monolignol biosynthetic pathways.^[2,14] Gymnosperm softwoods (e.g., *Pinus*, *Picea*, *Abies*) synthesize lignin almost exclusively from coniferyl alcohol, resulting in 'guaiacyl lignin' composed of >95% G-units with minor amounts (<5%) of H-units.^[6,33] Because G-units possess an unsubstituted aromatic C-5 position, softwood lignins undergo high degrees of intramolecular cross-linking during lignification, forming dense 5-5' and β -5' carbon-carbon bonds that impart high thermal recalcitrance.^[6,34] In contrast, angiosperm hardwoods (e.g., *Populus*, *Betula*, *Eucalyptus*) synthesize both coniferyl and sinapyl alcohols, producing 'guaiacyl-syringyl (G-S) lignin' with typical S/G ratios ranging from 1.0 to 3.0.^[2,35] The presence of methoxyl groups at both C-3 and C-5 in syringyl units blocks C-C coupling at C-5, favoring linear, ether-linked (β -O-4') polymer chains that are chemically more susceptible to depolymerization.^[35] Woody monocots and bamboos (e.g., *Bambusa*, *Dendrocalamus*) incorporate substantial amounts of p-coumaryl alcohol alongside G and S units, forming 'H-G-S lignin' characterized by significant ester- and ether-bound p-coumaric and ferulic acid pendant groups.^[14,36] Table 1 summarizes the key structural traits, linkage profiles, and molecular characteristics across woody taxonomic groups.

4.2. Chemical structures of monolignols and key

interunit linkages

To provide clear chemical elucidation, Fig. 2 presents the complete molecular structures of the primary monolignol precursors (p-coumaryl alcohol, coniferyl alcohol, and sinapyl alcohol) alongside the explicit chemical linkages that define the polymer backbone, including β -O-4' aryl ether, β - β' resinol, β -5' phenylcoumaran, 5-5' biphenyl, 4-O-5' diaryl ether, and β -1' diphenylpropane structures.^[6,32]

5. Advanced structural characterization techniques

Precise qualitative and quantitative characterization of lignin is essential for establishing structure-property-activity relationships.^[18,37] Given lignin's structural complexity, modern analytical strategies rely on a complementary suite of high-resolution spectroscopic, chromatographic, and mass spectrometric methods.^[18,19] Table 2 details the primary analytical methodologies, operational principles, key structural parameters resolved, and inherent analytical limitations. Although advanced analytical methodologies have substantially deepened our understanding of lignin chemistry, critical technical limitations hinder their routine application. State-of-the-art 2D ^1H - ^{13}C HSQC NMR provides unambiguous interunit linkage quantification (β -O-4', β - β' , β -5'), yet it suffers from heavy signal overlapping in the aliphatic side-chain region ($\delta_{\text{H}}/\delta_{\text{C}}$ 3.0 – 5.5/50 – 90 ppm) and requires complete sample solubilization—an ongoing challenge for highly condensed technical lignins without harsh chemical derivatization (e.g., acetylation). Quantitative ^{31}P NMR resolves aliphatic, phenolic, and carboxylic hydroxyl groups with precision (in mmol/g), but relies on moisture-sensitive phosphitylation reagents (e.g., 2-chloro-4,4,5,5-tetramethyl-1,3,2-dioxaphospholane, TMDP) that rapidly hydrolyze in trace water, leading to artifactual hydroxyl overestimation. Furthermore, the Size-Exclusion

Table 2: Advanced analytical techniques for structural elucidation, functional group quantification, and macromolecular profiling of lignin^[18,19,37,38]

Analytical Technique	Operational Principle	Key Parameters Resolved	Advantages	Limitations
2D 1H-13C HSQC NMR	Heteronuclear single quantum coherence cross-polarization	Quantification of β -O-4, β - β , β -5 linkages; H:G:S ratios; S/G ratio	Definitive fingerprinting of linkage profiles and aromatic units	Requires complete sample dissolution; overlapping signal region
Quantitative 31P NMR	Phosphitylation of hydroxyl groups using TMDP followed by 31P NMR	Precise absolute quantification (mmol/g) of aliphatic, phenolic (H,G,S), and carboxylic -OH	Unmatched resolution of distinct hydroxyl functional environments	Derivatization step required; moisture-sensitive reagents
Py-GC/MS	Analytical flash pyrolysis coupled with gas chromatography-mass spectrometry	Phenolic monomer profiling, guaiacyl/syringyl cleavage products, origin verification	Rapid micro-scale analysis; no complex sample prep needed	Secondary pyrolytic reactions can alter quantitative fidelity
SEC / GPC	Size-exclusion chromatography with UV/MALLS/RI detection	Molecular weight distribution (M_n , M_w) and polydispersity index (PDI)	Essential for macromolecular size profiling and fractionation	Apparent M_w depends on calibration standards and solvent association
FTICR-MS	Fourier-transform ion cyclotron resonance mass spectrometry	Ultra-high resolution molecular formula assignment of depolymerized fractions	Resolves thousands of individual molecular species simultaneously	High instrument cost; complex ionization matrix effects
FTIR / Raman	Vibrational spectroscopy of functional bonds	Identification of aromatic ring vibrations, carbonyl, and hydroxyl stretch modes	Non-destructive, rapid qualitative monitoring	Low quantitative precision due to broad overlapping bands

Chromatography (SEC/GPC) frequently overestimates molecular weight distributions (M_n , M_w) due to intermolecular aggregation via non-covalent π - π stacking in organic solvents, while Analytical Py-GC/MS yields incomplete quantification owing to secondary thermal cleavage reactions during flash pyrolysis. A combined multi-technique analytical protocol remains imperative to cross-validate linkage profiles and functional group quantities.

6. Commercial extraction processes and technical lignins

The chemical and physical properties of isolated 'technical lignins' are profoundly governed by the industrial extraction process.^[8,10] Commercial pulping processes modify native lignin structures through ether linkage cleavage, variable condensation reactions, and incorporation of non-lignin elements (e.g., sulfur).^[8,39] Table 3 presents a comparative critical analysis of major commercial and emerging isolation processes.

The commercial adoption of technical lignins is heavily governed by the chemical trade-offs inherent to each pulping process. While Kraft and Sulfite processes dominate industrial volumes due to established infrastructure, sulfur incorporation drastically restricts high-value application in catalytic refining and biomedical nanomedicine. Conversely, sulfur-free

processes such as Organosolv yield pristine, low-polydispersity fractions rich in reactive native ether linkages (β -O-4'), but their economic feasibility remains severely compromised by capital-intensive solvent recovery units and high operational expenses. Despite technical advancements in characterization, significant technological limitations persist. 2D HSQC NMR, while invaluable for linkage profiling, suffers from signal overlap in the side-chain region and requires complete dissolution in deuterated solvents a condition rarely met by highly condensed technical lignins without prior derivatization. Similarly, quantitative 31P NMR relies on moisture sensitive phosphitylation reagents that can hydrolyze, yielding inaccurate hydroxyl counts. On the extraction front, organosolv processes deliver high purity but are severely limited by high solvent volatility, solvent recovery energy demands, and equipment corrosion, which prevent widespread adoption over conventional, highly polluting kraft pulping.

7. Quantitative industrial and biological bioactivities

Lignin's multi-functional phenolic framework underpins a broad range of biological and industrial bioactivities.^[12,15] Rather than relying on qualitative descriptors, Table 4 and Table 5 provides explicit, peer-reviewed quantitative metrics evaluating antioxidant capacity, UV-shielding performance, antimicrobial inhibition, drug

Table 3: Comparative evaluation of major technical lignin extraction processes [8,10,39,40]

Process	Yield	Purity	Key Chemical Traits	Advantages	Technical Limitations
Kraft	High	Moderate	Contains 1.5 – 3.0% sulfur; highly condensed; hydrophobic	Industrially established (> 85% global production); cheap feedstock supply	Odorous sulfur contamination; high structural heterogeneity; dark color
Organosolv	Moderate	High	Sulfur-free; low M_w ; high reactive phenolic –OH	High chemical purity; preserved β -O-4' linkages; high reactivity	High organic solvent recovery costs; operational volatility; expensive
Sulfite / Lignosulfonate	High	Moderate	High sulfur (3 – 8% as –SO ₃ H); water-soluble	Direct water solubility; strong surfactant/dispersing agent	High inorganic ash and sugar impurities; sulfur content limits refining
Soda	Moderate	High	Sulfur-free; carboxylic acid rich; moderate condensation	Sulfur-free stream; well-suited for non-woody & hardwood feeds	Lower recovery yields from softwoods; variable ash content

delivery encapsulation, and agricultural functional efficacy across specific lignin forms.

8. Critical analysis, challenges, and future perspectives

While several studies report strong antioxidant (DPPH IC50 <15 µg/mL) and antimicrobial efficacy for organosolv and kraft lignins, conflicting findings exist in the literature. For instance, antioxidant performance varies drastically depending on the solvent system used for extraction, as residual hydrogen-bonding solvents can mask phenolic -OH reactivity. Similarly, reported antimicrobial MIC values range broadly from 0.25 mg/mL to >10 mg/mL. This discrepancy stems from inconsistent bioassay protocols (e.g., dispersion methods, particle size variations, and bacterial strains used) rather than intrinsic chemical differences alone. A systematic standardization of radical and microbial assay conditions is required to resolve these literature contradictions.

7.1. Antioxidant and free radical scavenging mechanisms

The antioxidant activity of lignin is primarily mediated by its phenolic hydroxyl groups, which readily donate hydrogen atoms to neutralize free radicals, forming stable, resonance-stabilized phenoxy radical intermediates. [15,41] Quantitative evaluations using 2,2-diphenyl-1-picrylhydrazyl (DPPH) and 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) assays demonstrate that low molecular weight, highly non-condensed organosolv lignin fractions exhibit superior DPPH IC50 values (9.2–15.4 µg/mL), performing comparably to commercial synthetic antioxidants like BHT (butylated hydroxytoluene).[41] Ortho-methoxyl substitution (characteristic of G and S units) further enhances radical scavenging capacity by stabilizing phenoxy radicals through electron donation and intramolecular hydrogen bonding.[15,40]

7.2. Antimicrobial efficacy and photoprotective uv-

shielding

Lignin-derived phenolic compounds exert potent antimicrobial action against Gram-positive (e.g., Staphylococcus aureus, Bacillus subtilis) and Gram-negative (e.g., Escherichia coli, Pseudomonas aeruginosa) pathogens.[43,44] Mechanisms include damaging bacterial cell membrane integrity, inducing intracellular oxidative stress, and lysing cell walls.[43] Minimum inhibitory concentrations (MIC) for organosolv and fractionated kraft lignins range from 0.25 to 1.00 mg/mL.[44] When incorporated as nanoparticles into active food packaging films (e.g., poly(lactic acid) or polyvinyl alcohol), lignin provides total UV-blocking (>98% UV-A and UV-B absorption) at low loadings (1–2 wt%), preventing photo-oxidation and extending food shelf life without compromising transparency.[16,42]

7.3. Agricultural valorization: controlled-release & soil hydrogels

Agricultural applications represent one of the most immediate, economically viable, and scalable non-combustion pathways for technical lignins.[45,46]

Controlled-release fertilizers (CRFs): Lignosulfonates and modified kraft lignins serve as hydrophobic, biodegradable barrier coatings for granular urea and NPK fertilizers. Coated urea granules delay nitrogen dissolution by 21 to 35 days, reducing nitrate leaching into groundwater by up to 45% and minimizing ammonia volatilization loss.[46]

- Soil conditioners and superabsorbent hydrogels:** Polymerized lignin matrices cross-linked with acrylic acid or vinyl monomers form superabsorbent hydrogel networks capable of increasing soil moisture retention by +32% in arid sandy soils. These networks chelate essential micronutrients (Fe²⁺, Zn²⁺, Mn²⁺), protecting them from premature soil immobilization and enhancing root uptake efficiency.
- Bio-based seed coatings:** Formulations combining LNPs with plant growth-promoting rhizobacteria or biopesticides form protective seed films. These

Table 4: Quantitative performance benchmarks of lignin formulations across industrial, biomedical, and agricultural bioactivities [13,15-17,41-46]

Functional Category	Lignin Type / Formulation	Principal Mechanism	Quantitative Performance Metric	Representative Reference
Antioxidant Activity	Organosolv Lignin Fraction (Low Mw, high phenolic -OH)	Hydrogen atom transfer (HAT) & single electron transfer (SET) to radicals	DPPH scavenging IC50: 9.2 - 15.4 µg/mL ABTS inhibition: >88% at 50 µg/mL	[15,41]
UV-Shielding / Photoprotection	Lignin Nanoparticles (LNPs) in PLLA / PVA films	Aromatic chromophore broad-spectrum absorption (UV-A & UV-B)	UV blocking: >98% at 2 wt% LNP loading Film SPF rating: 15 to 45+	[16,42]
Antimicrobial Activity	Fractionated Kraft Lignin & Copper-LNP composites	Cell membrane disruption, intracellular ROS generation, cell lysis	MIC vs <i>S. aureus</i> : 0.25 - 0.50 mg/mL MIC vs <i>E. coli</i> : 0.50 - 1.00 mg/mL	[43,44]
Drug Delivery Carrier	Self-assembled Hollow LNPs (Targeted delivery)	Hydrophobic core encapsulation & pH-responsive aromatic pi-pi stacking	Paclitaxel Encapsulation Efficiency (EE): 82 - 94% Drug Loading (DL): 12 - 18 wt%	[13,17]
Agricultural Applications	Lignosulfonate-coated Urea & Lignin Hydrogel Matrices	Slow diffusion barrier coating & high moisture retention chelating capacity	Nitrogen release delayed by 21-35 days; Soil moisture retention increased +32%	[45,46]

coatings shield seeds from soil-borne fungal pathogens via localized antimicrobial phenolic release while improving seedling germination rates under drought-induced oxidative stress.

8.1. Techno-economic feasibility and biorefinery scalability

Despite compelling laboratory-scale demonstrations, scaling technical lignin valorization to commercial operations faces severe techno-economic barriers.[7,8,47] High operational costs associated with organic solvent

recovery in organosolv processes and complex purification steps currently limit economic viability.[8] Furthermore, batch-to-batch structural heterogeneity derived from seasonal biomass variations and pulping fluctuations poses severe quality control challenges for industrial polymer formulators.[7,48] Scalability remains the single greatest bottleneck transitioning laboratory successes to commercial supply chains. While self-assembly protocols yield uniform LNPs at milligram scales using anti-solvent precipitation, scaling these processes to multi-ton industrial outputs leads to batch-

Table 5: Quantitative performance metrics of technical lignins and lignin nanoparticles (LNPs) across functional activities

Study / Lignin Type	Specific Formulation & Particle Size	Targeted Activity	Quantitative Metric & Baseline Value	Absorption Range / Load Efficacy
Kraft Lignin	Unfractionated powder (> 1 µm)	Antioxidant	DPPH radical inhibition: 65.4 – 78.2% (IC ₅₀ = 38.5 – 45.2 µg/mL)	N/A
Organosolv Lignin	Low M _w fraction (100 – 250 nm LNPs)	Antioxidant	DPPH radical inhibition: > 92.0% (IC ₅₀ = 9.2 – 15.4 µg/mL)	N/A
Acetylated Kraft LNPs	Nano-spheres (60 – 120 nm)	UV-Shielding / Photoprotection	UV blocking: 98.5% Film SPF rating: 15 – 45 + Encapsulation Efficiency (EE): 82 – 94%	Absorbs across full UV-A (315 – 400 nm) & UV-B (280 – 315 nm) spectrum
Alkali / Soda LNPs	Hollow spheres (150 – 220 nm)	Targeted Drug Delivery	Drug Loading (DL): 12 – 18 wt%	High hydrophobic drug entrapment (e.g., Paclitaxel, Aspirin)
Fractionated Kraft Lignin	Micro/Nano-colloids (80 – 180 nm)	Antimicrobial Activity	<i>S. aureus</i> MIC: 0.25 – 0.50 mg/mL <i>E. coli</i> MIC: 0.50 – 1.00 mg/mL	Cell lysis via intracellular ROS generation

to-batch aggregation, poor size reproducibility, and high wastewater generation. Furthermore, feedstocks suffer from severe seasonal and geographic heterogeneity. Variations in S/G ratios across raw biomass batches alter depolymerization yields unpredictably, making continuous, automated industrial processing extremely difficult to standardize. From an economic perspective, replacing low value on-site thermal combustion (evaluated at ~\$50–\$80 per ton as boiler fuel) with high value biomaterial conversion (potentially >\$1,000–\$3,000 per ton) requires substantial capital expenditure. The primary cost drivers in lignin valorization are downstream purification, organic solvent recycling, and sulfur removal. Until biorefineries achieve high-yield, closed-loop solvent recovery systems (>98% efficiency), the capital pay-back period for technical lignin refining remains uncompetitive compared to fossil-based polymer manufacturing.

8.2. Life cycle assessment (lca) and carbon footprint

While lignin is inherently bio-based, its environmental credentials must be verified through rigorous Life Cycle Assessment (LCA).^[49,50] Diverting kraft lignin from pulp mill recovery boilers to materials manufacturing requires replacing its thermal energy with alternative fuel sources, which can offset net carbon savings if fossil energy is utilized.^[49] Sustainable biorefineries must balance energy self-sufficiency with material recovery to achieve true net-zero carbon footprints.^[50]

8.3. Regulatory and translational barriers in biomedical applications

While lignin nanoparticles (LNPs) demonstrate promising *in vitro* paclitaxel encapsulation efficiencies (82 – 94%), high radical scavenging, and bioimaging fluorescence, assertions of immediate biomedical translation are significantly overstated. Currently, over 95% of published biomedical lignin studies remain confined to *in vitro* cell assays or small-animal (rodent) models. Virtually no lignin-based nanomedicine has advanced to Phase I clinical trials or achieved commercial regulatory approval by the FDA or EMA.^[17,51–54] The path to clinical translation is blocked by severe fundamental barriers:

1. **Polydispersity and heterogeneity:** Regulatory agencies require strict batch-to-batch chemical reproducibility, which is inherently difficult for a natural, heterogenous polymer.^[52–55]
2. **Toxic impurities:** Technical lignins contain residual sulfur, heavy metal catalysts, and organosolv residues that trigger immunogenic responses and cytotoxicity *in vivo*.^[56]
3. **Pharmacokinetics and accumulation:** Long-term *in vivo* biodistribution, metabolic degradation, organ accumulation, and renal clearance rates for non-water-soluble LNPs remain largely unmapped.^[57]

Claims of lignin's near-term viability in human targeted drug delivery, cancer therapy, or clinical diagnostics must be tempered by the necessity of multi-year, standardized toxicity and clearance evaluations. In

biomedical applications, despite high paclitaxel encapsulation efficiencies (82–94%) observed *in vitro*, transition to clinical settings is heavily hindered by regulatory frameworks (e.g., FDA and EMA).^[58,59] Technical lignins contain residual sulfur, heavy metals, and carbohydrate residues from extraction processes, which trigger immunogenic reactions *in vivo*. Regulatory bodies require precise structural definition and batch reproducibility for nanocarriers criteria inherently incompatible with lignin's natural polydispersity and variable cross-linking. To clear regulatory barriers, long-term pharmacokinetics, biodistribution, long-term tissue accumulation, and standardized Good Manufacturing Practice (GMP) isolation protocols must be established.^[60–62]

8.4. Standardization and future interdisciplinary outlook

Unlocking the full potential of lignin demands global standardization of technical lignin grades alongside interdisciplinary collaboration joining plant genetics, analytical chemistry, bioprocess engineering, and materials science.^[7,8,52] Metabolic engineering of woody crops (e.g., genetic tuning of S/G ratios or introduction of labile ester bonds via 'designer lignins') promises feedstocks optimized for effortless depolymerization.^[27,53] Simultaneously, expanding machine learning models to predict depolymerization yields from 2D HSQC NMR spectra will accelerate commercial process optimization.^[54,63,64]

9. Conclusion

Lignin-derived polyphenols represent an extraordinary, highly abundant renewable aromatic resource capable of driving the transition toward a sustainable bio-based economy. This review has provided a comprehensive, quantitative, and critical synthesis bridging woody plant taxonomy, phenylpropanoid biosynthesis, advanced analytical characterization (2D HSQC NMR, 31P NMR), and industrial process extraction. Quantitative bioactivity benchmarks clearly demonstrate lignin's high performance across antioxidant, antimicrobial, UV-protective, drug delivery, and agricultural domains. However, overcoming commercial scalability constraints, batch heterogeneity, environmental carbon trade-offs, and biomedical regulatory hurdles remains imperative. Through continued interdisciplinary innovation in green chemistry and metabolic engineering, technical lignins will undoubtedly emerge as indispensable precursors for next-generation biomaterials, active packaging, and sustainable chemical platforms.

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CRedit Author Contribution Statement

H. B. Roghan: Conceptualization, Data Curation, Formal Analysis, Investigation, Methodology, Visualization, Writing - Original draft, Writing - Review & editing. **S. Vennila:** Conceptualization, Methodology, Project Administration, Validation, Supervision, Writing - Review & editing. Both the authors have read and approved the final version of the manuscript for publication and agree to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Conflict of Interest

There is no conflict of interest.

Artificial Intelligence (AI) Use Disclosure

The authors declare that artificial intelligence (AI)-assisted tools were used only for language refinement, grammar improvement, and manuscript structuring purposes during the preparation of this work. All technical content, experimental implementation, results, and interpretations were independently developed and verified by the authors.

Supporting Information

Not applicable.

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