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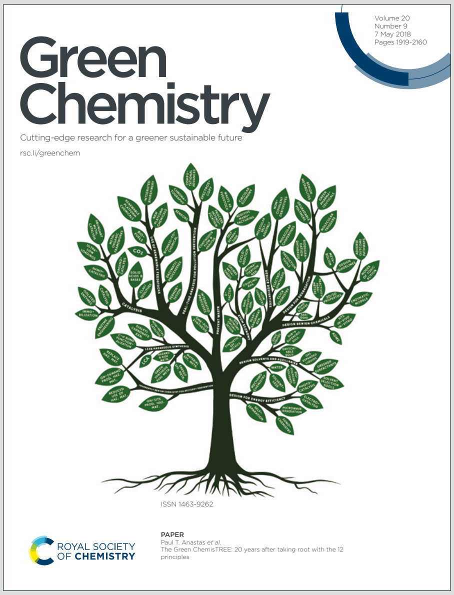

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PAPER

Bio-based platform chemicals synthesized from lignin biorefinery

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Bio-based chemicals synthesis by lignin offers a promising pathway of bioenergy utilization to achieve the target of the Paris Agreement with < 2°C of climate warming temperature. Recently, numerous efforts have been conducted in lignin biorefinery including lignin extraction, separation, depolymerization and products separation, among which each subprocess has a profound effect on overall process. The right configuration and integration implementation of biorefinery subprocesses determines the ultimate efficiency and cost. This review provides an in-depth mechanism understanding on subprocesses aiming to giving an enlightenment on right configurations and integration implementation of subprocesses and early commercialization of lignin biorefinery. This review includes: 1) elucidation of lignin biosynthesis pathway, 2) dissection of mechanism of biorefinery subprocesses with intelligible graphical overviews and summary, 3) analysis of tech-economic viability from the view of market potential and each biorefinery subprocess, and 4) discussion of challenge and perspective with the emphasis on gene engineering and start-up time of lignin-based bioenergy popularization. Present-day results indicate more efforts should be performed toward the gene engineering regulation and integration implementation of subprocesses to promote early commercialization of lignin biorefinery considering that delayed use of bioenergy may reduce carbon emission mitigation capacity and increase global food risk.

1. Introduction

Presently, conventional fossil fuels still dominate the global- scale energy network, of which coal, oil and natural gas supply accounted for 27.2%, 31.2% and 24.7% respectively in 2020 [1]. Undesirably, these resource reserves would be completely exhausted by 2069~2088 [2]. Simultaneously, the adverse gases like CO_2 released by combustion stage of these fossil fuels aggravate greenhouse effect, bringing along with great threat to ecosystem balance and human health [3]. Additionally, such carbon emission is also the main obstacle to achieve the central target of the Paris Agreement with limiting the global average temperature increase to well below 2°C [4]. As such, it is imminent to develop renewable resources with carbon-neutrality and sustainability as the substitute of conventional fossil fuels with insufficient reserves.

Currently, sustainable energy sources mainly involve wind, solar, hydro, nuclear, tidal and biomass energy [5], in which biomass energy is regarded as one of the most promising energy attributing to the advantage of carbon neutrality and widespread abundance [6]. Photosynthetic process, which is unique metabolic model for biomass, converts the solar energy into chemical energy and fixes CO_2 into key components of organism as vector of follow-up biomass energy derivative products like biohydrogen or biodiesel [7]. It was reported that over 200 billion tons of biomass was produced by photosynthesis each year [6]. The development history of biofuels is categorized as three generations and biomass material sources greatly vary with development stages. First-generation biofuel production adopted food crops like sugar beets, soybean, and canola as feedstocks. But given the reliance on food by human beings, it may pose a risk to invoking conflict between energy production and food demand [8]. Microalgae, as the feedstock of third-generation biofuel production, has the advantage of not rummaging the food chain and requiring arable land [9]. However, the high cost and water resource shortage aggravation caused by great freshwater requirement and algae separation are the major bottlenecks to hinder the popularization of algae-based bioenergy production process. Although using wastewater as medium is a promising solution for freshwater demand [10], the potential difficult or risk such as poor algae growth activity in wastewater with high loading of nutrients or toxic substance, microcystin release, algae separation, toxic substances migration from microalgae to food chain and so forth are the issues that need to be addressed urgently.

Conversely, lignocellulose biomass, as the feedstock of second-generation biofuel production, is the most abundant bioresource on the planet. Fortunately, cellulose and hemicellulose compositions of lignocellulose have been commercialized with considerable efforts. Whereas, lignin was frequently as cheap materials [11]. It was estimated that pulp mill generates about 50–70 million tons of lignin each year [12]. Of the by-product lignin, considerable proportion was abandoned or combusted while merely 2% of lignin was utilized for commercialization [12]. Thus, the low-value utilization of lignin results in an unexpected waste

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of resources and additional disposal costs. Undeniably, the abundant aromatic structure of lignin endows itself great potential and feasibility to produce high value-added chemicals [13]. Using lignin as a substitute of petroleum to produce chemicals not only realizes the lignin disposal but also decreases the demand for fossil fuels. Notably, the stubborn structure of lignin caused by cross-linked by free radical polymerisation between syringyl (S), guaiacyl (G), and *p*-hydroxyphenyl (H) units is the main challenge of lignin valorization into chemicals. Delightfully, various types of depolymerization strategies have been developed to flexibly produce various lignin-based chemicals [13, 14], suggesting a viable pathway to simultaneously realizes energy crisis mitigation and environmental protection.

Indeed, the conversion of lignin to high value-added chemicals is a multiple process that relies on delignification, lignin separation, depolymerization and products separation from the perspective of technical route [15-18]. Over the past few decades, considerable efforts have been contributed on these subprocesses, endowing the great significance and enlightenment in pursuit of the commercial application of value-added chemicals production by lignin. Undeniably, technical feature and mechanisms significantly vary with technologies. Also, every subprocess has a profound effect on overall process. Overall, understanding the mechanism and features of subprocesses are crucial for their right configurations and integration implementation in terms of the early commercialization of lignin biorefinery. Based on these considerations, a comprehensive mechanism analysis on lignin biorefinery subprocess is attempted in this review.

This review attempts to provide an in-depth mechanism dissection in lignin biosynthesis pathway and biorefinery subprocesses aiming to give the enlightenment and reference on right configurations and novel integration strategy development of subprocesses, and accelerate the commercialization process of lignin-based chemicals production. Concisely, this review is categorized as four sections: 1) the dissection of lignin biosynthesis pathway and primary structure, which is the foundation of lignin conversion, 2) the mechanism elucidation of biorefinery subprocesses, in which intelligible graphical overviews are provided to help the researcher easily access to an intuitive information, 3) the tech-economic analysis from view of a market potential and every biorefinery subprocess, and 4) the discussion of associated challenge and perspective in lignin biorefinery.

2. Biosynthesis pathway and primary structure of lignin

Lignin is a highly heterogeneous biopolymer formed by the oxidative polymerization of multiple phenylpropane units (Fig. 1) [19, 20], a termed lignification process that occurs in cell walls via phenoxy radicals created by the oxidation of phenolic OH-group initiated by laccase and peroxidase enzymes [21, 22]. Based on the variety of number of methoxy groups, these phenylpropane units are categorized as syringyl (S), guaiacyl (G), and *p*-hydroxyphenyl (H) units, which have two, one and zero methoxy groups in the benzene ring respectively [23]. Polymerization reactions relate to the combination or termination of two free radicals (Fig. 1), also known as supramolecular self-assembled chaos [22]. Consequently, lignin endows the plant cell wall with rigidity and mechanical strength against microbial attack and allow plant grow tall [24]. In addition, it also facilitates plant's nutrients and H_2O transport over long distance [23]. Notably, these phenylpropane units originate from the sinapyl alcohol, coniferyl alcohol, and *p*-coumaryl alcohol (*i.e.*, primary monolignols), which are produced via the phenylpropanoid pathway, a multi-enzyme biochemical grid consisting of copious of enzyme families and metabolites (Fig. 1) [23, 25-27].

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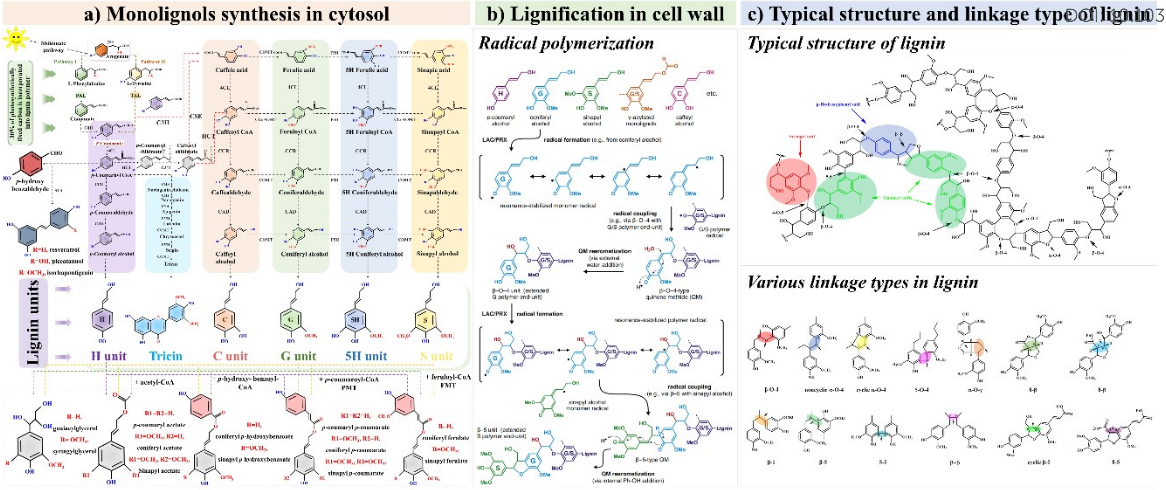

Fig. 1 Biosynthesis pathway of lignin. PAL: L-phenylalanine ammonia-lyase; TAL: L-tyrosine ammonia-lyase; C4H: cinnamate 4-hydroxylase; C3H: 4-coumarate 3-hydroxylase; C3'H: 4-coumaroyl shikimate/quinate 3'-hydroxylase; COMT: caffeate/5-hydroxyferulate 3-O-methyltransferase; F5H: ferulate 5-hydroxylase/coniferaldehyde 5-hydroxylase, 4CL: 4-hydroxycinnamate:CoA ligase; HCT: 4-hydroxycinnamoyl CoA:shikimate/quinate hydroxycinnamoyltransferase; CSE: caffeoyl shikimate esterase; CCoAOMT: caffeoyl CoA 3-O-methyltransferase; CCR: cinnamoyl CoA reductase; CAD: cinnamyl alcohol dehydrogenase; STS: stilbene synthase; PMT: *p*-coumaroyl-CoA monolignol monomer transferase; FMT: feruloyl-CoA monolignol transferase; CHS: chalcone synthase; CHI: chalcone isomerase; FNS: flavone synthase; F3'H: flavonoid 3'-hydroxylase; F5'H: flavonoid 5'-hydroxylase. (Fig. a) modified from [25, 26] with permission. (25: Copyright 2019, nature, 26: Copyright 2019, Elsevier)), Fig. b) reused from [28] with permission. Copyright 2019, Elsevier, Fig. c) reused from [29] with permission. Copyright 2022, Elsevier).

Concretely, the phenylpropanoid pathways are divided into Phe ammonia-lyase (PAL)-mediated and Tyrosine ammonia-lyase (TAL)-mediated pathway (in grass) (Fig. 1), which used L-phenylalanine (L-Phe) and L-tyrosine (L-Tyr) derived from the shikimate pathway as precursors, respectively [23, 25-27]. Besides, excess 30% of photosynthetically fixed carbon is incorporated into lignin biopolymer in this process [30]. Detailed illustration of phenylpropanoid pathway is delineated in Fig. 1. Although the substrates differ with the two pathways, they suggest the same end: *p*-coumarate synthesis. In contrast to PAL-mediated pathway, TAL-mediated pathway has low-energy requirement because the dehydroxylation process of aromatic ring of arogenate and the synthesis process of cinnamate to *p*-coumarate are bypassed [21]. Nonetheless, PAL-mediated pathway is more common in nature. This may be due to that the intermediate *trans*-cinnamic acid produced by PAL-mediated pathway is pivotal for the downstream metabolic process like benzenoid volatiles [21]. Also, the carbon flux regulation between PAL and TAL, and the physical association of PAL and the enzymes involved in phenylpropanoid pathway are also the key reasons to limit the TAL-mediated pathway [21]. Notably, some species like monocots contain bifunctional ammonia-lyase, which show the similar efficiency to PAL and TAL [31].

In terms of the biosynthesis of monolignols, it is achieved by stepwise reduction of the propanoid side chains and modifications of the benzene ring [25, 26]. In detail, monolignols synthesis starts with the deamination of L-Phe and L-tyrosine L-Tyr. Then, the carboxylic acid moiety of synthesized (hydroxylated) *p*-coumarate proceeds stepwise reduction steps to produce CoA-thioester, aldehyde, and alcohol in turn driven by a series of enzymes including 4CL, CCR and CAD (Fig. 1). It is worthy mentioned that the synthesis of coenzyme A (CoA) ester via 4CL causes the net loss of energy because of the ATP consumption [27]. Modifications of the benzene ring mainly include the hydroxylation and methylation of aromatic rings, which are initiated by CYTO-CHROME P450s (C4H, C3H and F5H) and methyltransferase (CCoAOMT and COMT), respectively [26]. After a series of reactions including deamination, hydroxylation, methylation and reduction, three primary monolignols (H, G and S) are formed [23]. These primary monolignols not only participate in the formation of lignin biopolymer but also can be used as substrates for further biosynthesis (Fig. 1). In addition to primary monolignols, some other monolignols are also formed like tricin, caffeyl alcohol and 5H coniferyl alcohol upon regulation of the phenylpropanoid pathway [26]. Notably, the supply and proportion of monolignols for lignification are regulated by metabolic flux, which significantly alter lignin amount and type [27]. Overall, lignification shows great flexibility to incorporate these various monolignols into lignin biopolymer, endowing the inherent plasticity in terms of lignin polymerization. Nonetheless, primary monolignols H, G and S still dominate in the composition of lignin biopolymer [23].

After biosynthesis in cytosol, these monolignols are transferred to the cell wall to accomplish the lignin polymerization, which relates to the combination or termination of two free radicals [22]. In such process, the monolignols secreted by lignifying cells or adjacent other lignifying cells and/or non-lignifying cells are initiated by localized oxidation systems in cell wall (*i.e.*, laccase/O_2 and/or peroxidase/H_2O_2) to achieve the combinatorial radical coupling, thereby producing the lignin biopolymer (Fig. 1) [28]. The core step of lignin polymerization is associated with so-called 'end-wise' polymerization, a cross-coupling reaction process between free radicals created by monolignols oxidation and free radicals created by free-phenolic ends of growing lignin biopolymers (Fig. 1)

[28]. Generally, the content of these monolignols significantly differs with plant taxonomy (Table 1) [32]. Typically, in softwood lignin, G unit occupies a considerable content comparing with S and H unit. Conversely, hardwood lignin mainly contains G and S unit. Lignin can incorporate various monolignols, but G and S units are always preferred when available [23].

Table 1. Relative content and BDE of primary units and inter-unit linkages in different type of biomass [32-35].

Monolignol/ Linkage	Softwood (%)	Hardwood (%)	Grass (%)	BDE (kcal/mol)
S	0	46-75	20-54	-
G	>95	25-50	33-80	-
H	<5	0-8	5-33	-
β-O-4	43-50	50-65	74-84	56.54-72.30
α-O-4	6-8	4-8	n.d.	48.45-57.28
4-O-5	4	6-7	n.d.	77.74-82.54
β-1	3-7	5-7	n.d.	64.7-165.8
β-5	9-12	4-6	5-11	125.2-127.6
β-β	2-4	3-7	1-7	-
5-5	10-25	4-10	n.d.	114.9-118.4
Others	16	7-8	n.d.	-

Given the monolignol's diversity, conjugated π-system, regiochemical arrangement of radical coupling steps and the change in the model of re-aromatization step of post-coupling quinone methide, numerous possible inter-unit linkages are created during lignin biosynthesis, mainly including the C-O-C and C-C bonds (Fig. 1) [28, 36, 37]. Table 1 illustrated the content and bond dissociation energy (BDE) of inter-unit linkage in various types of lignin. Obviously, the content of the same linkage significantly differs with various types of lignin. For example, hardwood lignin contains a higher β-O-4 content (50-65%) versus that (43-50%) in softwood lignin. A convincing explanation is that C_5 position in S units of hardwood lignin avoids the free radical coupling, which leads to a higher β-O-4 content [38]. On the contrary, attributing to the more G units in softwood lignin, the C_5 positions offers more chances to cause the C-C free radical coupling, thus producing more C-C bonds [39]. At present, lignin type can be divided into native lignin and technical lignin. For native lignin, the breaking of β-O-4 is thought to be the key step attributing to its higher content and weaker BDE. Conversely, technical lignin like Kraft lignin and Organosolv lignin undergoes a great structural modification, thereby causing a higher content of C-C bonds [22, 32]. Thus, the breaking of C-C bonds is regarded as the key step in the technical lignin. The higher BDE is the main limitation in depolymerization of technical lignin. Fortunately, gene engineering regulation may provide the opportunity to maintain the structural integrity in lignin extraction process, which helps to the improve the limitation caused by lignin extraction. Also, it is also possible to regulate the expression of lignin subunits from heterogeneous G/S type to homogeneous C type [40]. This is conducive to regulate the product's selectivity. In conclusion, more works in the future should be devoted to the gene engineering regulation of lignin by deeply understanding the metabolic pathway of lignin.

3. Extraction method on the modification of lignin structure

Lignin extraction is the core of the biorefinery since the extraction technique understandably has a profound effect on aromatic chemicals production in terms of variation on chemical structure and reaction of lignin. Lignin extraction can be divided into two ways: 1) direct delignification process in which lignin is extracted as a target from lignocellulose; 2) indirect delignification process in which lignin is liberated via conversion and solubilization of the carbohydrate. Compared with indirect method, direct method has drawn more extensive attentions. In this section, the effect of direct extraction methods on lignin structure are concretely analyzed (Fig. 2 Right). More points are illustrated in Table 2.

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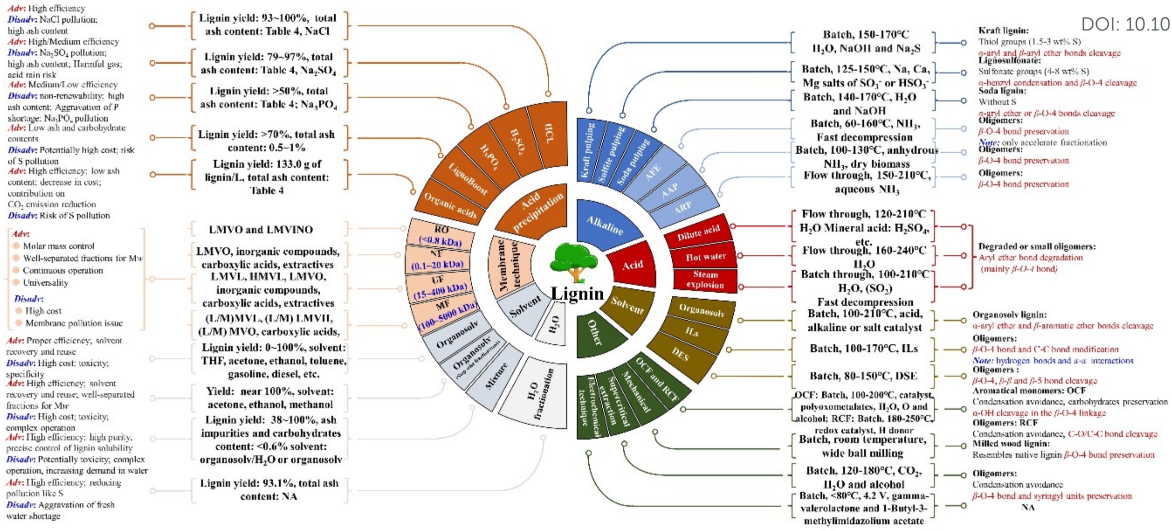

Fig. 2 (Left) Feature of various types of extracted lignin separation techniques and its advantages/disadvantages, and (Right) characteristic of various types of lignin extraction techniques and its effect on lignin structure. (*Note*: Adv: advantage, Disadv: disadvantage, AFE: ammonia fiber explosion/expansion, AAP: anhydrous ammonia pretreatment, ARP: ammonia recycled percolation, NA: Not analyze). *Note*: Right figure modified from [22] with permission. Copyright 2018, Royal society of chemistry.

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3.1 Alkaline extraction

Kraft pulping, which is also called as the sulfate process, is the most extensively employed for the pulping process, yielding excess 90% of all chemical pulps [22, 41, 42]. Benefits of Kraft process mainly originate from the superior lignin extraction capacity, preparation of high-purity pulp and self-sufficiency on energy requirements [34]. Kraft pulping is carried out in a solution called as white liquor consisting of NaOH and Na$_2$S under 150-170°C. Pulping selectivity can be significantly enhanced without simultaneously aggravating carbohydrate solubilization in such process, which is ascribed to the improved delignification caused by HS$^-$ in white liquor [22]. Pulping process is divided into three stages [41]. At initial stage, α-aryl and β-aryl ether bonds in lignin are broken under 80°C. Then, carbohydrates are stripped from biomass in the bulk stage, with the temperature range from 150°C to 170°C. Meanwhile, 70% of lignin is extracted in this stage within 80 mins. Finally, a constant temperature is maintained to obtain 90% of delignification [41]. Consequently, large amounts of black liquor that is rich in lignin and other components is produced. Nonetheless, the harsh condition usually causes the degradation and repolymerization of lignin. As such, the lignin separated from black liquor is highly condensed and accommodates less β-O-4, which is not conducive to the subsequent aromatic chemicals production process. Additionally, sulfur is incorporated on the side-chain of phenolic moiety as thiol groups in kraft pulping, making downstream valorization process complicated [42, 43]. Sulfite pulping was carried out in a solution consisting of sulfite or bisulfite under 125-150°C, mainly involving three stages: i.e., sulfonation, hydrolysis, and condensation [32, 44]. Sulfite pulping can be operated regardless of the pH. But it is determined by the selection of sulfite or bisulfite salt [22, 44]. During sulfite pulping, sulfonic group is introduced on the aliphatic side chain or reactive α position of phenolic moiety to form benzyl sulfonate groups [22, 45, 46]. Then, the bonds between lignin and carbohydrates are hydrolyzed to liberate lignin (lignosulfonate) with sulfonic groups. These sulfonic groups and other hydrophilic groups like carboxylic groups confer excellent water solubility property to lignosulfonates [22]. Likewise, lignosulfonates contain unaccepted sulfur content, which is higher versus Kraft lignin [22]. Also, condensation of α-benzyl ether during sulfite pulping forms relatively stable C-C bonds while β-O-4 content is decreased due to the degradation [44]. Conversely, soda pulping proceeds in a sulfur-free strong alkali solution (13%-16% of NaOH) under 140-170°C, totally avoiding the introduction of sulfur. Nonetheless, the alkaline depolymerization is less efficient in such process because of the absence of a strong nucleophile [44].

Apart from alkaline extraction based on sodium hydroxide, ammonia-based alkaline extraction techniques have also been studied. Ammonia-based alkaline extraction techniques are categorized into three types: (A) ammonia fiber explosion/expansion, (B) anhydrous ammonia pretreatment and (C) ammonia recycled percolation [22, 47]. The most benefit for these techniques is that ammonia can be recovered easily and β-O-4 bond is effectively preserved. During ammonia fiber explosion/expansion process, ammonia enters into the biomass driven by the explosive pressure release to alter the biomass structure such as decreased cellulose crystallinity, breakage of the ester linkages between carbohydrate and lignin as well as wall enhanced porosity caused by removal/redeposition of decomposition products of the cell wall [47]. Nonetheless, it is worthy noted that ammonia fiber explosion/expansion process doses not directly extract the biomass components and can only accelerate the subsequent lignin extraction. Another ammonia-based alkaline extraction technique was achieved via anhydrous ammonia. Liquid anhydrous ammonia, an outstanding cellulose swelling agent to infiltrate cellulose fibers even crystalline domains, can effectively interfere with the natural hydrogen bond network to form cellulose–ammonia complex. In turn, crystalline structure is modified by controlling removal of ammonia (evaporation) [47]. However, moisture content should be assured at low level since water hinders the formation of restructured cellulose, which is dissimilar from ammonia fiber explosion/expansion process. Additionally, anhydrous ammonia pretreatment does not need pressure release and can extract dissolved lignin under stable high pressure, which is so called as extractive ammonia pretreatment. Under this model, only minor lignin is degraded and the β-O-4 bonds are relatively intact. For lignin extraction based on ammonia recycled percolation, flowing aqueous ammonia solution continuously extracts lignin from biomass and quantities of hemicellulose is also extracted. Extracted lignin can be recovered by precipitation (ammonia evaporation). Even though the carbohydrates during lignin separation are also coprecipitated, it can be removed by mild acid catalyzed hydrolysis without altering lignin structure integrity [22, 47].

3.2 Acidic extraction

Acidic extraction is generally carried out by using either diluted acid solvent or concentrated acid solvent. Acids adopted in this process mainly include HCl (37-42%), HNO$_3$ (2%-4.4%), H$_2$SO$_4$ (50-80%), H$_3$PO$_4$ (82-84%) and organic acid like maleic or fumaric acids [48-52]. For concentrated acid-mediated extraction process, it was performed via two steps at the operating conditions of ~100℃ and atmospheric pressure [53]. Driven by concentrated acid, the structure of cellulose crystalline was first destroyed while the fiber was dissolved. Then, the glycosidic bonds were converted into monosaccharides through diluted acid. However, the high operating cost, equipment corrosion and potentially inhibition on downstream processing made this technique commercially unattractive. Diluted acid extraction is more popular in terms of industrial application since it was conducted with a 0.1~10% acid concentration [54]. In dilute acid extraction under batch model, cellulose and hemicellulose polysaccharide matrix were disrupted. Meanwhile, aryl ether linkages (mainly relates β-O-4 linkages) were broken and acid-insoluble lignin was recovered in the form of precipitation [55]. It is worthy mentioned that the condensation reaction and redeposit on the biomass surface were unavoidable under batch model, leading to a great modification for extracted lignin. These limitations can be overcome by the sequential extraction (SE) mode since the dissolved lignin is continuously transferred, which is conducive to the preservation of β-O-4 linkages [56]. By applying this model using *p*-toluene sulfonic acid as solvent, 83% of lignin with well-preserved β-O-4 linkages was successfully extracted. Importantly, the structure of carbohydrates also remains intact. Alternatively, endogenous acid can also be adopted to lignin extraction. Concretely, endogenous acid originates from the H$^+$ dissociated from water at high temperature and organic acids released from biomass [22, 57]. As with exogenous acid under batch model, lignin also experienced acidolysis and condensation but with a relatively low extent. It is considered that β-O-4 linkages were

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partially preserved in the endogenous acid-mediated lignin extraction. As the alternative acidic method, steam explosion pretreatment, which integrates the feature of diluted acid and ammonia fiber explosion/expansion pretreatment, was also adopted for lignin extraction. As with ammonia fiber explosion/expansion, this process only accelerates the subsequent lignin extraction.

3.3 Organosolv extraction

Organosolv extraction, featured by the advantages of high selectivity, nontoxic reagent organic, no sulfur contaminant and solvent recyclability, is accomplished based on the superior solubility in specific organic solvents. Additionally, the greatest advantage in such process is the multicomponent component separation of lignocellulose, i.e., lignin, hemicellulose and cellulose [44, 47, 58]. The common organic solvents for lignin extraction contain methanol, ethanol, acetone, n-butanol, formic acid, methyl isobutyl ketone, isopropanol and H_2O/organic co-solvents. Concretely, organosolv extraction can be categorized into alcohols-mediated and organic acid-mediated extraction. Alternatively, the combination of organic solvents and acid, alkaline or salt catalyst is also applied for lignin extraction (*i.e.*, catalytic extraction). During organosolv extraction, α-aryl and β-aryl ether bonds are broken down, leading to the extraction of lignin. Driven by small inorganic acid catalyst, α-aryl ether bonds are easier to break versus β-aryl ether bonds. Additionally, organosolv extraction also can be conducted in neutral and alkaline media. In alkaline media, β-aryl ether bond is the main broken linkage. As for neutral media, the generated acetic acid and furfural in reaction system are used as catalyst to accelerate the lignin extraction. It is worthy mentioned that lignin depolymerization and condensation are unavoidable in either case, which caused the decrease of β-O-4 bond and formation of oligomeric fragments. Lignin condensation is induced by the formation of active benzyl carbon cation or oxygen atom connected with benzyl since these intermediates are conducive to build a bond with the electron-rich carbon atom in the benzene ring of another lignin units [59]. The structural variation strongly relies on the process severity. To preserved-well β-O-4 linkage, concentrated alcohol is a feasible option since the incorporated alkoxy groups at the α-site of lignin's alkyl chains pose a prevention for β-O-4 linkage breakdown and lignin condensation [60]. Another viable strategy is to stablize intermediates by using proper agent like formaldehyde. Acetal is formed by reacting formaldehyde with α- and γ-hydroxy groups of the alkyl side-chains in β-O-4 [61]. Thus, the formation of reactive carbocation is effectively inhibited. Additionally, electron-rich meta sites are also partially blocked because of the formation of *m*-hydroxymethyl groups. However, the removal of formaldehyde incorporated into the residual carbohydrate pulp in subsequent steps should be considered.

3.4 Ionic liquid extraction

Ionic liquid, consisting of anions and cations, have drawn extensively attraction in terms of lignin extraction because of the advantages of superior capacity for destruction of lignocellulosic structure, recyclable and environmentally friendly [62-64]. These anions and cations can selectively destroy lignocellulosic structure. According to the discrepancy on ionic liquid selectivity, lignin extraction from biomass by ionic liquid was divided into two cases: i.e., ionic dissolution and ionosolv pulping [65]. In detail, for ionic dissolution, lignocellulose substrate can be totally solubilized. Cellulose is firstly recovered from mixture precipitation arisen from antisolvent (i.e., aqueous–organic solution or organic) before lignin precipitation [66]. Another great benefit of this process is that de-crystallization of cellulose is potentially conducive to downstream valorization process [67]. In dissimilarity to ionic dissolution, only lignin and hemicellulose can be dissolved while cellulose component keeps in the form of a solid pulp during ionosolv pulping. Then, lignin was recovered by precipitation caused by antisolvent [68]. As such, ionic dissolution is more recognized to be employed for lignin extraction due to its compatibility with second-generation ethanol biorefinery. To date, ionic liquid types for lignin extraction mainly include protic and aprotic ionic liquid, in which protic ionic liquid has been widely used for lignin extraction due to the superior performance [69]. But the cost and synthesis still need to be considered. During ionic liquid extraction, the extraction and dissolution of lignin can be explained by the strong interaction between ILs and lignocellulose [58, 63, 69]. These interactions mainly include hydrogen bonds, π-π or n-π interactions, electrostatic forces and van der Waals forces, in which hydrogen bonds and π-π or n-π interactions are considered as the main force to extract and dissolve lignin. The established hydrogen bonds between lignocellulosic and anion of ILs competes with the inter hydrogen bonds of lignocellulose, thus highly efficient cleaving the three-dimension networks in lignocellulose. The competing moieties of hydrogen bond formation mainly occur on the hydroxyl, carbonyl and carboxylic of lignocellulosic. H_2O can be used as anti-solvent to precipitate extracted lignin attributing to that the interaction between H_2O and ILs is strong versus that between ILs and lignin. The π-π and n-π interactions between cations of ionic liquid and aromatic moieties in lignin is another reason to extract lignin. Lignin contains large amounts of aryl carbons (>66%) associated with π electron, which is conducive to the formation of π-π. Compared with cations, anion part of ILs is also play a more vital role in the lignin dissolution since the anion endows the alkalinity while the π-π caused by cations of ILs contributes to enhance the lignin extraction efficiency [63].Notably, unproper cations or anion selection in ionic liquid could cause the high condensation degree of acquired lignin [65]. Cleavage of *β-O-4* bond and modification of C-C bond led to an enhancement for phenolic hydroxyl group and decrease for aliphatic hydroxyl group [70]. It hinders the subsequent chemical products. In contrast, *β-O-4* bond can be effectively retained by using the cations with short alkyl chains to substitute the cations with longer alkyl chains [62]. Overall, ionic type selection is crucial for aromatic chemical products production process unless other applications are considered. Additionally, other considerations or limitation, such as acid-base ratio, organic solvents, cost, toxicity, viscosity and recyclability also need to be continuously concerned and addressed in future work [63, 71, 72].

3.5 Deep eutectic solvents extraction

Deep eutectic solvents (DES) have drawn extensive attraction as a new generation of green solvents in lignin extraction in recent years because it can overcome the potential limitation of ionic liquid [73]. DES is made up of solvent mixtures of Lewis or Brønsted acids that consists of various anions/cations configuration [74]. It combines the advantages of ionic liquids and organic solvents [75]. DES was initially coined in 2003 to define the solvent system consisting of hydrogen bond donor like quaternary ammonium salts and acceptor like

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alcohols or carboxylic acids [76-78]. Such system constitutes a liquid driven by strong hydrogen-bonding interactions, decreasing the crystallization ability of the substrate. DES can selectively extract lignin or hemicellulose from biomass driven by mild acid-base catalysis mechanism while ether bonds between phenyl propane units are broken [78, 79]. Whilst cellulose is relatively intact, which is extremely beneficial for subsequent production of paper or bio-ethanol [78]. By using DES to pretreat biomass for cellulose and lignin extraction, enzymatic digestibility of cellulose was increased by 41.5% versus the case of untreated biomass [80]. Additionally, the co-precipitation of lignin and DES can be avoided because DES can well mixed with hot water, thus improving the purity of lignin. The extracted lignin by DES method has also been verified to have the advantages of well-preserved structures and low molecular mass distribution [58, 75, 81]. However, it is still worthy mentioned that the effect of DES on lignin structure depends on the functional groups of DES structure, viscosity, temperature and time, etc. [77, 78]. There are still huge gaps need to be filled, continuous work is required to identify the ideal DESs type for lignin extraction.

3.6 Other extraction

Other extraction methods such as supercritical extraction and electrochemical extraction are also used [22, 82, 83] . Supercritical fluid has ability to extract lignin from biomass attributing to the nonpolar and null surface tension under critical conditions. Recently, supercritical extraction technology has been adopted to extract lignin in eucalyptus fiber [83]. Comparing to the ethanol extraction method under high temperature, supercritical fluid consisting of CO_2, ethanol and water further enhanced the lignin extraction efficiency. During lignin extraction, physical and chemical processes simultaneously occur. Supercritical fluid has high permeability to cell walls. Also, the fast discharge favoured the separation and dissolution of lignin. Most importantly, the formaldehyde formed by CO_2 and ethanol avoids the condensation of lignin fragments. Acquired lignin poses high content of β-O-4 bond [83]. In addition, electrochemical technique was also applied for the lignin extraction. By applying electrochemical technique using organic solvents as medium, 66.7% of lignin was successfully extracted from lignocellulose below 80°C driven by hydroxyl radical produced from electrochemical process [82]. Notably, the contribution from organosolv treatment on lignin extraction cannot be ignored. Elucidating the interaction of organosolv extraction and electrochemical extraction on lignin extraction and identifying the extraction mechanism are essential for more extensive application of this technique. Also, the in-depth information about structural modification should be studied. Notably, a great advantage for supercritical extraction and electrochemical extraction is the no sulfur contaminant. Especially, electrochemical extraction can also be integrated with electrochemical depolymerization in single operating unit with milder operating conditions. Nonetheless, the information about the structural modification during lignin supercritical extraction and electrochemical extraction is still severely scarce. More work needs to be continuously performed to reveal the structural characteristics of lignin after these extraction processes.

3.7 Summary

Up to now, numerous methods have been developed to extract lignin from biomass for lignin-based chemicals production. Among these extraction techniques, mechanical extraction is thought to be simple in operation and conducive to obtain the valuable information about lignin structural modification in lab scale. However, this technique is unattractive in commercial application because of its time-consuming operation and high device requirement. By comparison, the alkaline lignin such as Kraft lignin produced from pulp and paper industry by alkaline extraction can be directly used as the substrate for lignin-based chemicals, which greatly reduces the investment of extraction process in whole biorefinery chain. However, the high BDE of C-C bonds formed in this process increase the difficulty in the subsequent aromatic chemicals production. Similarly, acidic extraction and organosolv extraction are also accompanied by these problems. In addition, the equipment corrosion caused by acidic extraction and high cost resulted from organic solvents need to be effectively addressed in pursuing further development of these techniques. In order to overcome the adverse effect of C-C bonds on lignin depolymerization, OCE and RCE provide promising and viable method but the principle varies with them. Simply, in OCE process, lignin condensation can be avoided by the methoxylation of α-OH in the β-O-4 linkage. For RCE process, hydrogen or small molecules is adopted to stabilize intermediates to prevent lignin condensation. Another great benefit for OCE and RCE is to provide the possibility to achieve the simultaneous lignin extraction and depolymerization in one pot. Still, the problems about the overoxidation in OCE and sustainability of hydrogen use in RCE should be carefully considered. Likewise, ILs and DES extraction also provide the chance on simultaneous lignin extraction and depolymerization. But some considerations or limitations, such as cost, toxicity, viscosity and recyclability also need to be continuously concerned and addressed. Recently, electrochemical extraction has drawn ongoing attention since electrochemical extraction proceeds under mild conditions and no other contamination. Most importantly, it builds a bridge between extraction, depolymerization, upgrading and product separation, showing a great potential in terms of whole lignin biorefinery chain. Nonetheless, a great challenge to hinder the development of this technique is still input cost. At present, copious of works have highlighted that using the renewable energy such as wind energy and solar energy as electricity supply can reduce the input cost, but the renewable energy cannot be directly embedded into the electricity grid attributing to variability and intermittency of renewable energy [84, 85]. In addition, the use of energy storage systems with reducing intermittent will further elevate the cost. Different power generation technique still showed relatively higher cost, such as 0.258-0.602 \$/kWh for PV, 0.166 \$/kWh for wind energy and 0.510 \$/kWh for solar energy [86]. To sum up, regardless of the techniques, considerable efforts need to be continuously performed to solve the technical limitations and decrease the investment cost to achieve the economic viability of lignin extraction step.

Table 2. Comparison of different extraction techniques on lignin extraction performance, structural modification and advantages/disadvantages.

Extraction technique	Raw material	Reaction condition	Delignification degree or yield	Structural modification	Advantages	Disadvantages	Ref
Alkaline extraction (Soda)	Sofia grass	Tem: 140℃, Time: 90 min	50.5%	\	• No sulfur contamination • Less inhibitory compound formation	• High cost • Great structural alteration	87
Alkaline extraction (Kraft)	Hibiscus cannabinus core	Tem: 170℃, Time: 180 min	20.75%	Methoxy group count: (1.47/Ar) Hydroxyl content: (1.34/Ar)	• Superior lignin removal • Low ash content • Smaller particle size	• Sulfur contamination • Long reaction time	88
Alkaline extraction	Eucalyptus alkali lignin	Tem: 180℃, Time: 15 min	26%	Total *β*-O-4 Untreated: 61.2 % Ar, Pretreated: 30.8 % Ar	• High sustainability • No extra reagent	• Low efficiency • Excessive water consumption	89
Steam explosion	Aspen	Tem: 185℃, Time: 5 min	10%	Total *β*-O-4 Untreated: 54% Ar, Pretreated: 42% Ar	• No sulfur contamination • Without reagent requirement • Shortened reaction time • Low ash content (<4%)	• High Hemicelluloses concentration • Great structural modification	90
Diluted acid	Rape straw	Tem: 130℃, Time: 60 min	17.9%	\	• Milder condition • High solubility for lignin • Shorter time demand	• Low conversion rate • High carbohydrate content • Severe device corrosion	91
Acid-catalyzed Steam explosion	Corncob residue	Tem: 90℃, Time: 8 h	57.3%	46% of *β*-O-4 preservation	• No sulfur contamination • High purity (99%).	• Extra reagent demand • Long reaction time	92
Organosolv extraction (Ethanol)	Switchgrass Lignin	Tem: 190℃, Time: 60 min	61%	Total phenolic OH Untreated: 0.86 mmol/g lignin Pretreated: 1.90 mmol/g lignin	• Elevated phenolic OH content • Soluble of lignin in alkali solution • Short reaction time	• Addition separation step for solvent • High cost • Hydrophobic lignin	93
Ionic liquid	Birch	Tem: 110℃, Time: 12 h	26%	Total *β*-O-4 Cellulolytic lignin: 65% Ar,	• No sulfur contamination • Slight structural modification	• High cost • Requirement of adding antisolvent to biomass regeneration	94

				Ionic liquid lignin: 56% Ar, Residual lignin: 59% Ar		● Viscosity issue	
DES	Rice straw	Tem: 60℃, Time: 12 h	60%	\	● High purity ● Reduced crystallinity index ratio for cellulosic	● High solvent cost ● Viscosity issue ● Long reaction time	95
Supercritical extraction	Eucalyptus short fiber	Tem: 180℃, Time: 60 min, Pressure: 15 MPa	35.9%	Higher *β*-O-4 bond content (80.43%)	● Potential carbon emission reduction ● *β*-O-4 bond preservation	● High energy consumption ● Extra reagent demand ● Strict equipment requirement	83
Electrochemical extraction	*Eucalyptus obliqua* sawdust	Potential: 4.2V, Tem: 65℃, Time: 24 h	66.7%	\	● No sulfur contamination ● Milder condition ● Without reagent requirement ● Low energy input	● Overoxidation of lignin ● Difficult in incorporation of renewable energy into power grid ● Long reaction time	82

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4. Separation of extracted lignin from biomass

Numerous works have been conducted to produce lignin for further application such as chemicals or carbon fibers synthesis [96]. The molar mass of solubilized lignin fragments is the result that determined by extraction technique, raw material and used analysis method [97]. Consequently, the released lignin fragments usually have a quite heterogeneous molecular mass distribution compared with *M*w, hindering the subsequently effective utilization [98]. In general, lignin application scenarios vary with its molecular mass. Low *M*w lignin with abundant reactive functional groups like phenolic hydroxyl group and ortho-methoxy groups is considered as the high antioxidation performance material since these groups endow lignin with radical-scavenging properties [99-102]. Especially, the phenolic hydroxyl group was regarded as the main structural descriptor to determine antioxidant activity of lignin via proton coupled electron transfer mechanism, which reflects the free radical scavenging ability [101]. While, high *M*w lignin is usually used as the raw material of carbon fibers synthesis due to the high mechanical properties [96, 103]. As such, the separation of extracted lignin is essential to obtain specific molecular lignin fragments for further application. Currently, reported separation methods mainly include precipitation, membrane separation, solvent separation, of which concrete feature and working principle are depicted in Fig. 2 (Left) and Fig. 3. In this section, the principles and characteristic of various separation methods are highlighted rather than tedious elaboration of similar cases. More points are illustrated in Table 3.

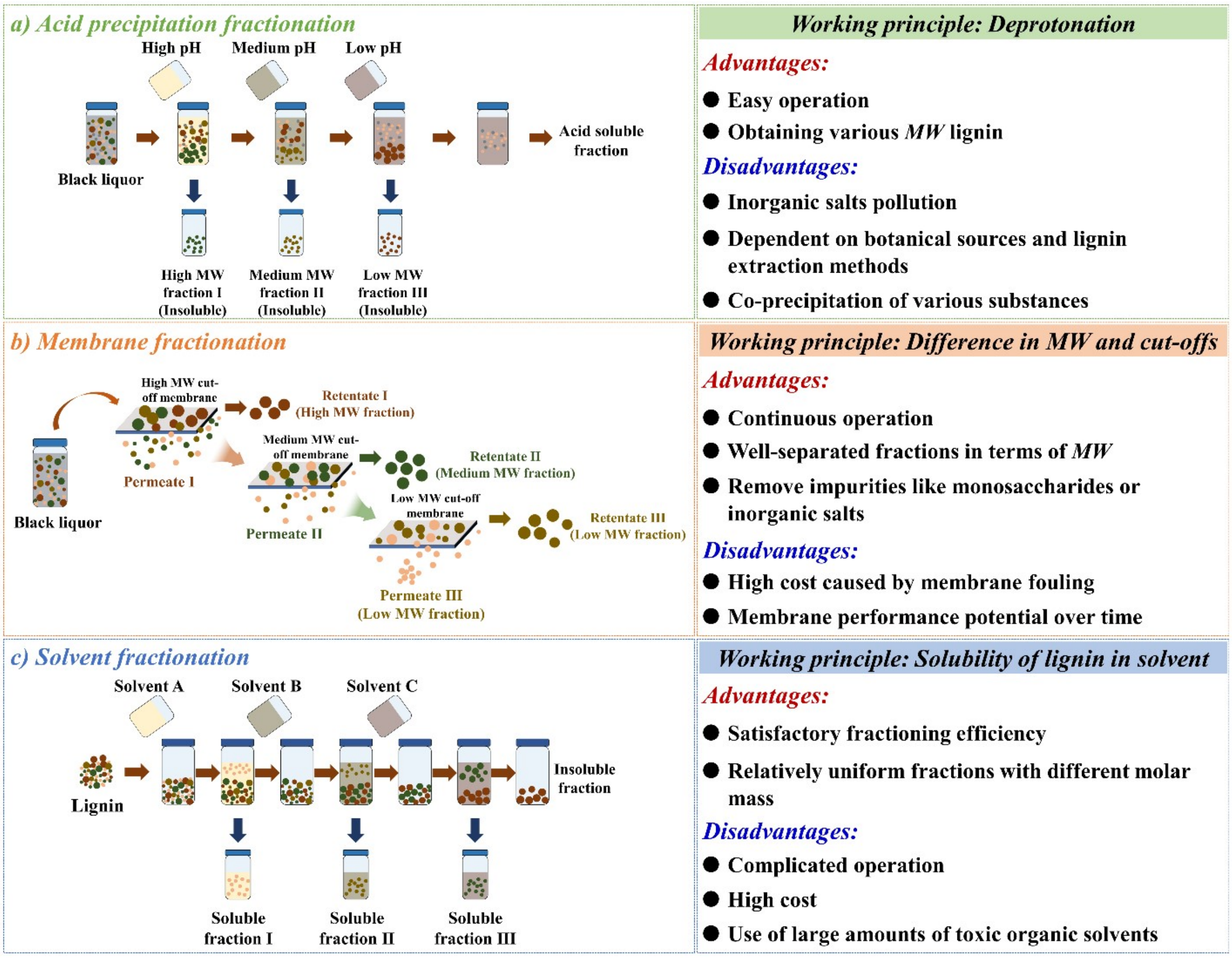

Fig. 3 Working principle and advantages/disadvantages of various separation techniques. (*Note*: this picture only reflects the working principle of separation techniques and did not reflect the actual separation steps, modified from [104] with permission. Copyright 2020, Royal society of chemistry.

4.1 Gradient acid precipitation

Acid precipitation is a simple and common method for the separation of lignin obtained from alkali-extraction process like pulping [103, 105]. By using this method, excess 90% of Kraft lignin can be fractionated from black liquor [105]. Generally, acid precipitation is performed by using inorganic acids (CO_2, H_2SO_4, HCl, H_3PO_4, etc.) or organic acid (acetic, lactic and citric acid, etc.) [96, 105-107]. Lignin has featured as high alkali solubility attributing to the ionization of the phenolic and carboxyl groups, whose negative charges form the inter-molecules electrostatic repulsive [108]. Additionally, due to the negative charge on the surface of colloid, stable colloid structure is formed [109]. Reducing pH is conducive to protonation of these groups and increasingly decrease the electrostatic interactions within the solution. Simultaneously, van der Waals and other hydrophobic forces will dominate, which causes progressive self-aggregation of the lignin [110, 111]. Consequently, colloidal precipitation is created. During acid precipitation, various molecular mass of lignin fragments can be recycled by varying acid gradients (altering the pH). Concretely, high molecular mass lignin (HMWL) exhibits a higher p*Ka* values and lower solubility. As such, it is first precipitated at the initial stage of adding acid (higher pH) versus low molecular mass lignin (LMWL) [110]. In other words, HMWL contained the lower negative charge than LMWL, giving them the poor stability over LMWL. With the increasing addition of acid, the negative charge on the surface of the colloid is continuously neutralized by H^+. Attributing to the higher negative charge on surface of the colloid with LMWL, it exhibits a stronger stability than HMWL [98].

Separation of lignin by acid precipitation is the multifactorial process that relies on the molecular mass, pH, temperature, ionic strength and operating model, significantly affecting the precipitated lignin yield [98, 103, 105, 106, 112, 113]. Concretely, HMWL (20 kDa retentate) can be totally precipitated under higher pH and shows a narrow range of precipitation pH compared to LMWL. Also, precipitation rate is significantly enhanced attributing to the higher Zeta potential and larger particle size created by HMWL [98]. Reducing pH causes the gradual decrease in the *M*w and polydispersity of separated lignin. Besides, the separated lignin' yield is continuously enhanced [98]. Likewise, lower temperature is also conducive to the enhancement of lignin separation yields. This is because that p*Ka* of lignin is increased under lower temperature, thus decreasing the lignin solubility [112]. On the contrary, ionic strength should be increased in terms of enhancing the lignin separation yields. Higher ionic strength is conducive to decrease the range of inter-molecules repulsive interaction [112]. As such, the attractive force between lignin molecules become dominative, promoting the progressive aggregation of lignin [112]. Operating model is another vital factor to affect the lignin precipitation yield. Comparing with the selective precipitation in a specific pH, a sequential precipitation by continuously reducing the pH exhibits a higher lignin precipitation yield [114].

It is worthy mentioned that the selection of acid type is vital since unproper acid utilization will cause unexpected negative effects like lignin contamination, environment pollution and aggravation of resource shortage. Concretely, Lignin precipitated with HCl will be contaminated with NaCl [105]. Likewise, the use of H_2SO_4 also accompanied by the issue of lignin contamination (Na_2SO_4). Also, it has the risk of harmful gases and acid rain phenomena formation [105, 106]. Due to the non-renewable nature of phosphate rock, continual consumption of H_3PO_4 significantly accelerate mineral resource shortage [115]. Analogously, phosphate salts are created in lignin precipitation due to its low solubility [116]. Thus, these limitations need to be carefully considered even though lignin can be effectively precipitated by these inorganic acids. By contrast, organic acids as a promising alternative for the lignin precipitation has been studied because of their non-toxicity and renewability, with a higher precipitation yield, low ash and carbohydrate contents for citric and lactic acids than H_2SO_4 under batch model [106]. However, it is noted that the lignin precipitation yield may be also lower than H_2SO_4 because of the differences in raw material [117]. "LignoForce" and "LignoBoost" are mill-proven technology for the kraft lignin separation. "LignoForce" is a process that associated with fibers removal, black liquor oxidation, lignin precipitation by CO_2 acidification, coagulation or aging, and wash by water and H_2SO_4 [118]. This process can obtain purified lignin of 60%, with about 1% of ash. Also, the obtained lignin contains a little sulfur since most of the odorous sulfur compounds are oxidized into non-volatile species. For "LignoBoost" process, pH is firstly reduced to 8~9 by CO_2 followed by H_2SO_4 is used to further lower the pH to 2~4 [106]. By this process, highly purified lignin of >70% is obtained from black liquor (data originates from Valmet), with the ash of 0.5–1% [119]. A potential benefit in this process is that the waste gas from industry can be tried as CO_2 source, not only decreasing the cost but also making a great contribution to carbon emissions reduction. Nonetheless, the waste gas should be carefully purified. Overall, considerable efforts about the development of lignin acid precipitation still need to be performed toward efficiency, purity, non-toxic, low cost, environmental friendliness and sustainability.

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4.2 Solvent separation

Solvent separation is another method to separate lignin originated from various sources. In principle, it is realized according to the difference on solubility of various molecular mass of lignin in single or mixed solvent [104]. Generally, the capacity of separating lignin is associated with the hydrogen bonding ability and Hildebrand solubility parameter [104, 109, 120]. Concisely, the ability of solvent to dissolve lignin is positively related to hydrogen bonding ability. Based on Hildebrand theory, the lignin solubility ability in specific solvent is determined by the similarity of Hildebrand solubility parameter between lignin and solvent [104, 109]. Comparing with HMWL, LMVL can be dissolved in a broader range of Hildebrand solubility parameter and hydrogen bonding capacity [121]. However, the limitation of Hildebrand solubility parameter should be emphasized since it does not consider the hydron bonding interactions. In terms of solubility ability, it is regarded as the contribution of nonpolar/dispersive interactions, dipole–dipole interactions and hydrogen bonding interactions [104, 109]. As such, Hansen solubility parameters considering the contribution of above three factors is thought to be more effective to reveal dissolving capacity [104, 122]. In order to determine the proper solvent that is used for lignin separation before workflow, Flory-Huggins polymer-solvent interaction parameter can be used to determine the lignin solubility in specific solvent [123]. Usually, solvent separation of lignin is conducted under room temperature and short reaction time [124]. Then, soluble part and insoluble residue are separated via centrifugation or filtration. In this method, widely used solvents mainly include ethyl acetate, alcohol, acetone, γ-valerolactone, 2-methyl tetrahydrofuran, ILs and DES [104, 109, 125, 126].

At present, solvent separation can be categorized as single solvent-mediated one-step separation, multiple solvents-mediated successive separation, mixed solvents-mediated successive separation and organic solvents/water mixture-mediated successive separation [47, 97, 104, 109, 127]. In detail, one-step separation is regarded as the simplest to operate. It can use solvents with different properties to separate the lignin stream into soluble and insoluble fractions (two types of lignin fraction with various molecular mass). Still, this method is limited by the molecular mass range of separated lignin. Multiple solvents separation provides a better option to separate lignin stream into narrower and lower dispersibility fraction. But it complicates the separation process. To overcome this issue, mixed solvents-mediated successive separation was used. In principle, the solubility of mixed solvent is manipulated by altering the ratio of two solvents with high and low lignin solubility ability.

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By contrast, this method not only achieves the accurate separation of lignin but also avoids the cumbersome operation steps. Nonetheless, the high toxicity of organic solvents is a problem that need to be solved immediately. Alternatively, H_2O provides a substitute to reduce the use amount of organic solvent. Likewise, the solubility of mixed solvent is regulated by altering the ratio of organic solvent and H_2O. Notably, potential risk of the water source shortage intensifies caused by excessive water consumption from this process should be seriously considered.

Although different strategies have been evolved to deal with the existing limitations, it is realized at the expense of novel issues. Consequently, the balance on environmental effect, economic benefit and processing performance caused by these advantages and disadvantages of old and novel strategies should be evaluated with caution. Also, attributing to the diversity of lignin structure and solvents as well as environmental risk caused by organic solvents, more right and advance separation strategies should be tailored with the aid of in-depth mechanism understanding of lignin solubility ability in various types of organic solvents.

4.3 Membrane separation

Membrane separation techniques (MST) have been widely applied in various scenarios, mainly including wastewater treatment and resource separation [128, 129]. Likewise, it is also applied in the biorefinery processes such as lignin separation and products separation [130, 131]. Detailed information about products separation based on MST is dissected in Section 6. In contrast to acid precipitation and solvent and H_2O separation, lignin separation based on MST has the advantages of continuous operation, no demand of extra chemical agents, satisfactory ability to couple with other techniques, the possibility of acquiring a purer stream in term of high value-added products, no requirements of regulating pH and temperature [16, 98, 130, 132-134]. In addition, a great benefit for MST is that various lignin fractions can be separated from black liquor attributing to the different cut-offs resulting from microfiltration, ultrafiltration, nanofiltration and reverse osmosis (Fig. 3) [135]. By principle, MST employs a semipermeable membrane as barrier to selectively separate two or more components according to the difference in molecular mass [130, 136]. The used membrane material mainly includes polymeric and ceramic, with a significant difference in feature [109, 137]. Comparing with the polymeric, ceramic can be applied in extreme conditions attributing to the higher chemical and thermal resistances while the order of selectivity is reverse [109, 130]. Notably, feed stream flow model significantly varies between traditional filtration and membrane filtration. Concisely, traditional filtration is perpendicular flow while membrane involves the cross-flow mode (*i.e.*, the feed stream flows tangentially on the membrane surface) [130].

At present, MST can be categorized as microfiltration (MF), ultrafiltration (UF), nanofiltration (NF) and reverse osmosis (RO), which can intercept the molecular mass with the 100~5000 kDa, 15~400 kDa, 0.1~20 kDa and <0.8 kDa, respectively [135]. Among MST, UF is commonly applied in lignin separation since the molecular mass of the technical lignin is generally inside the membrane cut-offs range of UF [130], such as soda lignin (1,000~3,000 g/mol (up to 15,000g/mol)), Kraft lignin (1,500~5,000 g/mol (up to 25,000g/mol)), hydrolysis lignin (5,000~10,000 g/mol) and organosolv lignin (500~5,000 g/mol), lignosulfonates (1,000~50,000 g/mol (up to 150,000g/mol)), and ionic liquid lignin (2,000 g/mol) [138]. By applying the membrane with various cut-offs, lignin fraction with different molecular mass range can be acquired. Concretely, the lignin fractions with a molecular mass higher than membrane cut-offs is remained in the retentate, simultaneously with a trace of LMWL. Whereas, remaining lignin across membrane into another side (permeate), without the existence of HMVL [98]. Notably, the high-purity lignin with uncondensed structures can be obtained in the low cut-offs' (5 kDa) permeate, indicating that the obtained lignin can be used as the vital source for chemicals production [136]. Still, membrane fouling is unavoidable in lignin separation. Especially, this fouling rate is further enhanced when using the lower cut-offs' membrane even though the purer permeate can be acquired [135, 139]. That is to say, the direct use of low cut-offs' membrane causes a fast occurrence of membrane fouling. Besides, the separated lignin in retentate still presents broader molecular mass range. Sequential membrane separation by membranes tandem (cut-offs of high to low) strategy offers a promising strategy to mitigate membrane fouling because membrane separation starts with high cut-offs' membrane [136]. Additionally, it allows to separate more various type of lignin fraction with different molecular mass ranges in a sequential operation.

Still, high loading of NaOH and impurities in lignin solution extracted by alkaline will seriously reduce the lifetime of membrane [98]. Although the membrane tandem strategy can mitigate membrane fouling to some extent, at the expense of higher operation costs. Undeniably, it further hinders the commercial application of MST. Using MST as post-pretreatment to combine with solvent extraction may be conducive to membrane fouling mitigation since pretreatment can reduce the lignin molecular mass and solution complexity [16, 140]. Importantly, lignin of low molar mass in lignin-lean black liquor (non-precipitating fraction after acid precipitation treatment of lignin) can be further effectively recycled [16]. Likewise, different fractions of lignin of different molecular masss can be obtained by two-step process of first organosolv pretreatment followed by UF [140]. Also, MST is also used as an auxiliary tool to guide the construction of other lignin separation strategy. For example, Wang et al. adopted UF to separate lignin fraction with different molecular masses and explore its effect on lignin acid precipitation to tailor the gradient acid precipitation strategy [141].

Notably, the extent or effectiveness of MST on lignin separation depends on operating parameters as the cut-offs of membrane used, feed concentration and the membrane flux [142-144]. To maximize membrane separation efficiency, the more in-depth mechanism about interactive effect of these factors on lignin separation efficiency should be explored. Most importantly, the main limitation of MST is still the membrane fouling since it causes sharp drop in membrane flus. Membrane fouling can be categorized as reversible fouling caused by concentration polarization and irreversible fouling resulted from pore blocking, partial clogging and solute adsorption [144]. Reversible fouling can be removed by washing while loss of permeability in irreversible fouling cannot be recovered [144]. As such, in pursing of lignin separation based on MST, the mechanism of membrane fouling should be carefully dissected to guide the construction of membrane fouling control strategies.

4.4 Summary

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Undeniably, the technical features or limitations significantly vary with separation techniques. Detailed information is delineated in Fig. 2 and 3. Acid precipitation is considered as the easiest in operation. It can separate lignin fraction with different molecular mass by altering the pH. However, a great limitation is that precipitation fraction contained extremely high ash content attributing to the formation inorganic salt (like NaCl, Na_2SO_4 and Na_2PO_4) although they have featured as the superior separation performance. High ash is not conducive to the chemicals production process. Organic acids can decrease the ash content to some extent, but its use on more types of feed stream should be continuously explored to determine the applicability. Also, the use of organic acids at the expense of higher cost. By contrast, commercialized "LignoBoost" process (typical representative company: Valmet) is still promising regardless of lignin precipitation yield/purity or environmental protection (carbon emission mitigation). Solvent separation has ability to separate different molecular mass lignin based on the differences of different lignin fraction in solubility of various organic solvents. Comparing with acid precipitation, solvent separation presented a lower polydispersity in separated lignin fraction. Nonetheless, the high toxicity and cost caused by organic solvents are the main drawbacks. For membrane separation, it may be unproper to directly treat raw black liquor with high concentration of NaOH and impurities because of the membrane fouling issue. Also, to mitigate membrane fouling, the understanding on mechanism of membrane fouling formation is necessary. Overall, the "LignoBoost" separation, solvent separation and membrane separation all can separate different molecular mass lignin based on their respective separation characteristics, with a low ash content. Nonetheless, a single technology is difficult to achieve complete separation of lignin. As such, it can be reasonably postulate that constructing a lignin separation chain including "LignoBoost" separation, solvent separation and membrane separation may have a great potential to recover all the lignin fraction, with a more narrowing molecular mass range (lower polydispersity) and higher purity (low ash content). Notably, it is more proper to place membrane separation unit at the end of the entire lignin separation chain considering membrane fouling, as the case of wastewater treatment plants. Still, the specific construction method of such lignin separation chain and its performance, economic benefits and life cycle need to be further explored.

Table 3. Typical cases about the lignin separation yield and ash content by various separation techniques.

Approach	Raw material	Acid/solvent/ membrane type	Operating condition	Lignin separation yield	Ash content (%)	Ref
Acid precipitation	Black liquor	HCl (2M)	pH=2 (Batch model)	16.15 g/L	28.23	116
	Black liquor	HCl (2M)	pH=4 (Batch model)	15.63 g/L	27.16	116
	Black liquor	H_2SO_4 (20%)	pH=2 (Batch model)	17.77 g/L	28.36	116
	Black liquor	H_2SO_4 (20%)	pH=4 (Batch model)	16.60 g/L	28.3	116
	Black liquor	H_3PO_4 (20%)	pH=2 (Batch model)	22.19 g/L	46.15	116
	Black liquor	H_3PO_4 (20%)	pH=4 (Batch model)	21.60 g/L	29.98	116
	Black liquor	"LignoBoost" process (Valmet)	First CO_2 followed by H_2SO_4	>70%	\	Valmet company
	Black liquor	CO_2 (acid wash)	pH=8.9 (Batch model)	69%	0.9	119
	Black liquor	CO_2 (H_2O wash)	pH=8.9 (Batch model)	69%	9	119
	Black liquor	H_2SO_4	pH=2 (Batch model)	96.26%	\	105
	Black liquor	H_2SO_4	pH=4 (Batch model)	95.17%	\	105
	Black liquor	H_2SO_4	pH=6 (Batch model)	94.71%	\	105
	Black liquor	HCl	pH=2 (Batch model)	96.78%	\	105
	Black liquor	HCl	pH=4 (Batch model)	93.46%	\	105
	Black liquor	HCl	pH=6 (Batch model)	95.42%	\	105
	Kraft lignin	Acetic acid	pH=3.6 (Batch model)	133.0 g/L	0.07	106
	Kraft lignin	Citric acid	pH=5.1 (Batch model)	118.4 g/L	1.99	106
	Kraft lignin	Lactic acid	pH=4.2 (Batch model)	133.1 g/L	1.02	106
	Steam explosion lignin	H_3PO_4	Stepwise (pH: 9-7-5-3-0.3)	54.84%	\	96
	Black liquor (Initial)	H_2SO_4	Stepwise (pH: 10.5-5-2.5)	79.1%	0.81	145
	Black liquor (Bulk)	H_2SO_4	Stepwise (pH: 10.5-5-2.5)	84.1%	0.81	145
	Black liquor (Residual)	H_2SO_4	Stepwise (pH: 10.5-5-2.5)	92.6%	0.84	145
	Alkali-extracted lignin	HCl	Stepwise (pH: 5.3-4-2)	99.99%	\	98
	Kraft lignin (hardwood)	HCl	Stepwise (pH: 9-7-5-3-1)	100%	20.9	114
	Kraft lignin (softwood)	HCl	Stepwise (pH: 9-7-5-3-1)	99.99%	41.1	114
Solvent separation	Parent CELF lignin	H_2O	Room temperature 24 h	93.1%	\	146
	Parent CELF lignin	Toluene	Room temperature 24 h	96.7%	\	146
	Parent CELF lignin	Ethanol	Room temperature 24 h	39.8%	\	146
	Norwegian spruce kraft lignin	EtOAc, EtOH, MeOH, and acetone	Stepwise: 2 h	99.9%	8.1	147
	Eucalyptus grandis kraft lignin	EtOAc, EtOH, MeOH, and acetone	Stepwise: 2 h	100%	15.5	147

	Liriodendron tulipifera milled wood lignin	Ethyl acetate, 2-butanone, methanol, acetone, and dioxane/water	Stepwise: 2 h	100%	\	148
Membrane separation	Softwood weak Kraft liquor	Ceramic ultrafiltration membrane	>10 kD	94.4%	\	149
	Mixed wheat straw/Sarkanda grass lignin	Two membrane cascade ultrafiltration	Stepwise: > 5 kDa, 5 kDa – 2 kDa, < 2 kDa	74.92%	\	150

Note: The extremely high ash content of the first 6 cases was also attributed to the high silica content (7.3%) and ash content (9.6%) in raw wheat straw in addition to contamination.

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5. Reaction mechanism of various depolymerization techniques

5.1 Enzymatic depolymerization

Despite lignin is featured as recalcitrant to chemical degradation, numerous microorganisms like bacteria and white-rot fungi that have ability to degrade lignin have evolved in nature [151, 152]. The degradation ability of these microorganisms on lignin ascribes to the secreted extracellular enzymes, mainly relating to laccase (Lac), lignin peroxidase (LiP), manganese peroxidase (MnP) and Versatile peroxidase (VP) [151, 153-155]. Lac is considered as a green catalyst since it utilizes O_2 as the activators to depolymerize lignin, with H_2O as byproduct. In general, Lac weighs 50~300 kDa and is composed of consecutive three cupredoxin domains with β-barrel symmetry [151]. According to its functions, Lac can be categorized into three types (*i.e.*, degradation of biopolymers, ring breakage of organics and cross-linking of lignin monomers). As delineated in Fig. 4, the four copper atoms in three cupredoxin domains play a vital role in Lac-mediated lignin depolymerization [151]. Correspondingly, the three copper active sites are divided into T1, T2 and T3 types. Concretely, T1 with a copper atom, also called as substrate reducing site, is the reaction starting point of lignin depolymerization, determining the maximum redox potential of Lac [153]. Attributing to its low redox potential, Lac can only oxidize phenolic subunits such as polyphenols and methoxy-substituted phenols [153, 156]. On the other hand, T2 with a copper atom shows the coordination ability on H_2O. As for T3 with two copper atoms, it is responsible for the H_2O splitting [151]. Notably, the catalytic limitation caused by the low redox potential of T1 can be overcome by using several catalytic redox species mediators to increase system's oxidation capacity. Currently, the found mechanism in Lac-mediated lignin oxidative reaction includes e^- transfer and H atom transfer mechanisms. Concisely, e^- transfer mechanism is associated with the radical cation creation by capturing electron from substrate. Whereas, H atom transfer is related to the radical creation via simultaneous capture of H atom and e^- from substrate [157, 158].

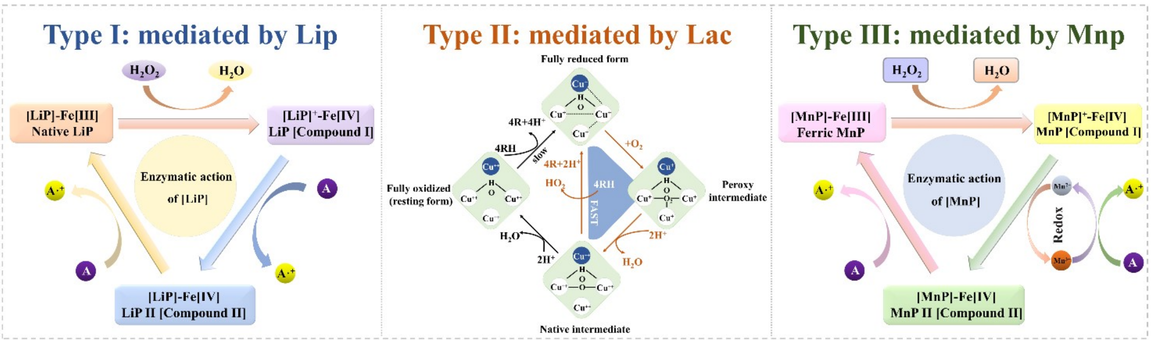

Fig. 4 Reaction pathway of enzyme-mediated lignin ECO (modified from [153-155] with permission. (153: Copyright 2022, Elsevier, 154: Copyright 2021, Elsevier, 155: Copyright 2020, Elsevier).

Conversely, LiP and MnP utilize H_2O_2 rather than O_2 as activators to achieve the lignin depolymerization[154, 155, 159]. LiP weighs 40~68 kDa and can oxidize phenolic subunits like vanillyl alcohol catechol and non-phenolic subunits like diarylpropane and *β*-O-4 lignin dimers [151]. Also, comparing with the non-phenolic subunits, the oxidation of phenolic subunits is more favorable in terms of reaction rate. As delineated in Fig. 4, the reaction process of LiP-mediated lignin oxidation includes three steps. Firstly, Fe(III) in ferric enzyme [LiP]-Fe(III) is oxidized to $Fe(IV)^+$ driven by H_2O_2. Afterwards, it is reduced to Fe(IV) by capturing the electron in initial lignin substrate. Finally, the Fe(IV) is reduced to native state by further capturing the electron in second lignin substrate [154]. Similarly, MnP shows an analogous reaction mechanism to LiP. The reaction was initiated by binding H_2O_2 with resting ferric enzyme. MnP weighs 40~50 kDa and can oxidize *β-O-4* bond in phenolic subunits and C_α-C_β bonds in non-phenolic subunits of the substrate [151, 154]. Likewise, VP, as the LiP and MnP isozymes in term of molecular mass, has dual oxidative ability with low to high redox potential, phenols dyes replaced and Mn^{2+}. It shows similar catalytic cycle to LiP and MnP [151]. By contrast, VP, combing the catalytic features of LiP and MnP, can oxidize both phenolic subunits and non-phenolic subunits without any mediators even in the absence of manganese [151].

Notably, the repolymerization resulting from phenoxy radicals should be seriously considered when developing the enzyme-mediated lignin depolymerization. Additionally, to protect enzyme from inactivation, the operating parameters like pH and O_2/H_2O_2 concentration need to be cautiously regulated for precisely catalytic depolymerization of lignin. Due the low redox potential, more efforts should be performed toward the integrating techniques to exert the respective advantages.

5.2 Electrochemical depolymerization

Lignin electrochemical conversion includes electrochemical oxidation (ECO) and electrochemical reduction (ECR), in which ECO is usually employed for lignin depolymerization while ECR is generally adopted to upgrade lignin derivatives like bio-oil. Regardless of ECO or ECR, the reaction essence is the electron transfer between the substrate and electrode. Concretely, both ECO and ECR can be categorized as two ways: *i.e.*, direct reaction and indirect reaction. Electron transfer mechanism and reaction type is delineated in Fig. 5. ECO reaction types of lignin are divided into four types. Type I relates the direct de-electron reaction of lignin. Type II to IV involves the indirect reaction mediated by reactive oxygen species and electrocatalytic redox species containing molecule and enzyme. As for ECR, direct ECR involves direct electronation-protonation of lignin without H_{ads} participation (Type I). Conversely, indirect ECR of lignin is associated with H_{ads} (*i.e.*,

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electrochemical hydrogenation or hydrogenolysis (ECH)) and electrocatalytic redox species (Type II). More detailed information involving cases evolution and mechanism understanding about the ECO and ECR depolymerization of lignin can be found in our recent review [29].

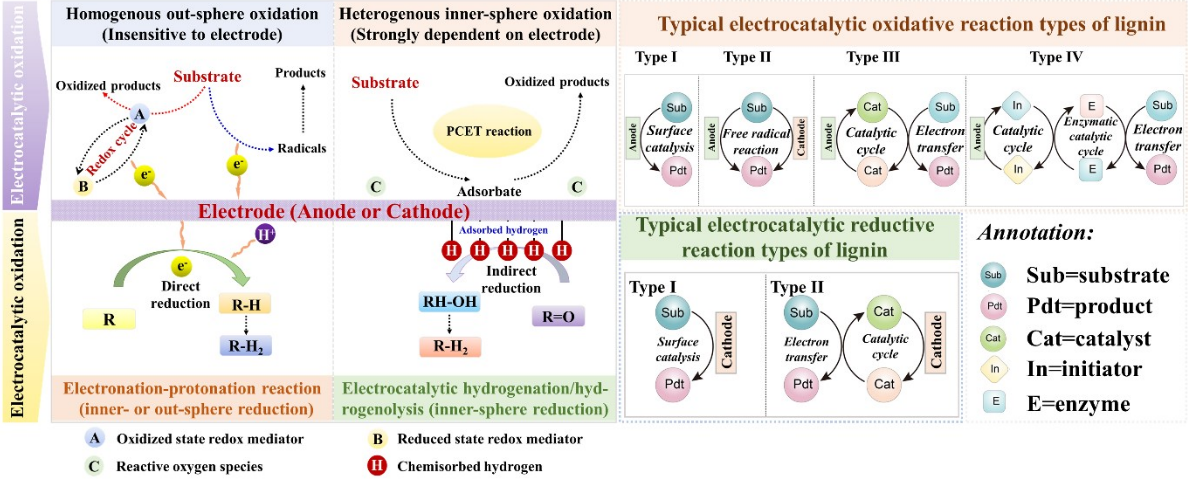

Fig. 5 Typical electron transfer mechanism and reaction types of lignin ECO and ECH (modified from [29] with permission, Copyright 2022, Elsevier).

5.3 Thermal depolymerization

Thermal depolymerization can be categorized as pyrolysis, hydrothermal liquefaction, and solvent liquefaction. Pyrolysis occurs in no or limited oxygen atmosphere [160]. It can be categorized as fast pyrolysis, intermediate pyrolysis, and slow pyrolysis based on the difference in heating rate and residence time [160]. In general, lignin pyrolysis undergoes three phases: *i.e.*, dehydration phase (~200°C), initial pyrolysis phase (200°C~400°C) and second pyrolysis phase (above 400°C), as delineated in Fig. 6 [161, 162]. Concretely, dehydration phase mainly involves dehydration reaction (<200°C), but quantities of gas like CH_4, CO_2 and CO will be also formed at this phase (around 150°C) because of the occurrence of demethoxylation, demethylation, and decarboxylation reactions between terminal functional groups and the branches [162, 163]. Concrete temperature of bond cleavage at initial stage is as follows: 1) α- and β-aryl-alkyl-ether bonds cleavage (150°C~300°C), 2) aliphatic chains rupture (300°C), methoxyl groups cleavage (310~340°C), and 4) C–C bonds cleavage (300~400°C) [164]. At this stage, copious of lignin monomers like syringol and coniferyl alcohol are obtained [165, 166]. It is noted that repolymerization reaction will occur when hydrogen donors are sufficient. Whereas, repolymerization will be inhibited at >350°C since the hydrogen released by lignin can be used as stabilizing agent of reactive intermediates [167]. Second pyrolysis phase relates to the decomposition of residual lignin and secondary reactions of primary products [162]. These reactions include gas formation, side-chain cleavage, rearrangement, functional group destruction, bond of hydroxyl or methylated groups and aromatic units, polymerization and carbonization [162, 168]. Notably, some physicochemical phenomena such as liquid intermediates formation and thermal ejection of oligomeric products may occur at this phase [162]. This also alters the formation and the feature of volatile products and thus affect the distribution of products in lignin pyrolysis.

Reaction mechanisms of lignin pyrolysis are discussed via two aspects: *i.e.*, initial pyrolysis phase and second pyrolysis phase. For initial pyrolysis phase, homolytic reaction is most recognized reaction mechanism [169-171]. Additionally, collaborative decomposition reaction mechanism such as Hoffmann reaction and Maccoll elimination are also probably occur due to its lower activation energy than that of free radical reaction [162, 172]. The required energy of initial reaction significantly varies with the linkage types (Fig. 6) [162]. Notably, Claisen rearrangement cannot occur in α-O-4 model compound pyrolysis even though the required energy for Claisen rearrangement and free radical reaction is approximative, which differs with the explanation statement of Hoffmann reaction and Maccoll elimination reaction that occur in β-O-4 model compound pyrolysis [162]. This is because that the rate constant of Claisen rearrangement is far less than that of free radical reaction (three orders of magnitude) [162]. Fig. 7 illustrated the typical reaction mechanism of β-ether-type dimers to produce the C_α=C_β and C_α=O compounds in lignin pyrolysis. On the one hand, C_α radical were created by the hydrogen abstraction of phenolic OH. On the other hand, phenoxy radicals were created by the hydrogen abstraction of C_α-H [173].

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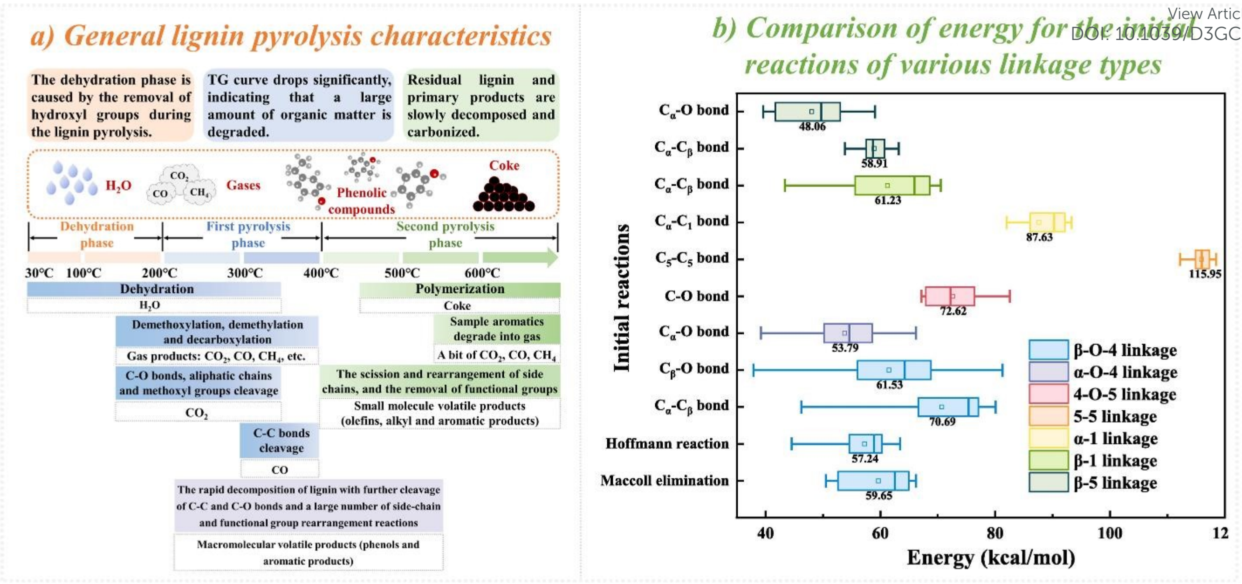

Fig. 6 a) General lignin pyrolysis characteristics and b) comparison of energy for the initial reaction of various linkage types. Reused and modified from [162] with permission. Copyright 2022, Elsevier.

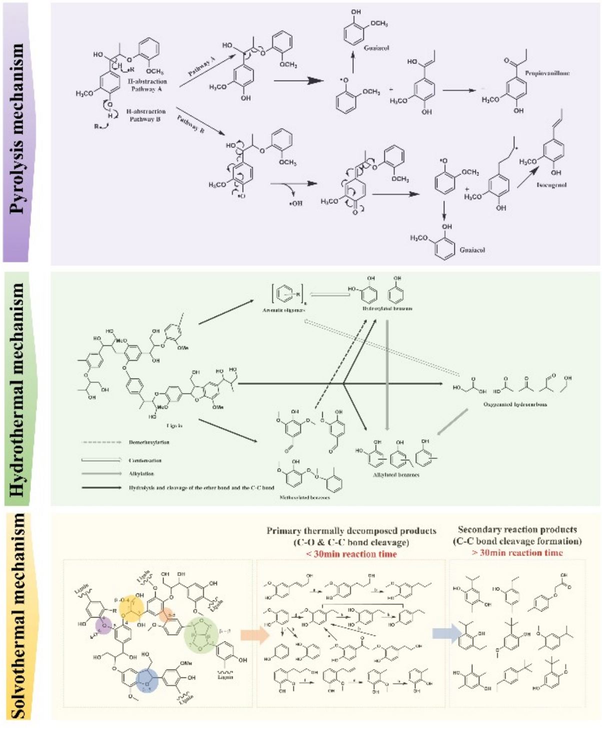

Fig. 7 (Top) Typical reaction mechanism of β-ether-type dimers in pyrolysis, (Middle) reaction pathways of lignin hydrothermal liquefaction, and (Bottom) solvothermal reaction mechanism for lignin with ethanol and formic acid. Modified from [174-176] with permission. (174: Copyright 2021, Elsevier, 175: Copyright 2021, Elsevier, 176: Copyright 2018, Royal society of chemistry.)

In lignin second pyrolysis phase, the reaction of lignin valorization into chemicals mainly relates to the side-chain conversion and oxygen-containing functional groups conversion. The reaction mechanism of side-chain conversion mainly involves the dehydrogenation (or dehydroxylation), free radical reaction, collaborative decomposition reaction and rearrangement reactions [177, 178]. Likewise, free radical reaction mechanism-mediated pyrolysis process biased to break the bonds of lower activation energy as the main reaction. Collaborative decomposition reaction and rearrangement reactions can overlap in side-chain conversion. By contrast, collaborative decomposition mechanism is more favorable than that of the rearrangement reaction and more reasonable explanation for the products distribution [177, 178]. For oxygen-containing functional groups (mainly includes hydroxyl and methoxy), it is converted by demethylation, dehydrogenation, and hydrogenation mechanism [179, 180]. In term of free radical reaction, demethylation reaction is more advantageous than dehydrogenation due to lower energy requirement. However, hydrogenation is the most dominant mechanism among three reaction mechanisms since the addition of hydrogen can greatly reduce the energy requirement (only occupy about 10% of demethylation reaction) [179, 180]. Overall, driven by these reaction mechanisms, these primary products in previous phase are converted to secondary products, including gases, volatile products and coke.

Compared with pyrolysis, hydrothermal liquefaction and solvent liquefaction are conducted under relatively mild operating temperature and pressure. Also, solvent's option is greatly different between these two processes [13, 14, 181]. Concretely, water and OH^-/H_3O^+ originating from water dissociation were adopted as the solvent and homogeneous acid/base catalysts respectively in hydrothermal liquefaction (HTL). Whereas, the water property significantly varies with temperature and substrate solubility increases with increasing water density [182, 183]. This indicates that lignin/water ratio regulation should be performed based on the solubility ability of water at different temperature. HTL of lignin mainly includes following processes: hydrolysis, ether and C-C bonds cleavage, cleavage and degradation of methoxy on the aromatic ring, and alkylation of groups on the aromatic ring [175]. Detailed reaction pathway was delineated in Fig. 7. Generally, ether bonds are easier to cleavage than C-C bonds but aromatic ring was unaffected by hydrothermal reaction [184]. Additionally, the methoxy of aromatic ring and the alkyl groups on

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the α-carbon are conducive to decrease the required time and increase the conversion rate of ether bonds like *α*-O-4 and *β*-O-4 [185, 186]. Notably, the HTL reaction pathway of lignin is competitive reaction between bond cleavage and condensation reactions, which results in a poor yield of aromatical chemicals. Fortunately, solvent liquefaction provides a promising option to avoid the condensation reactions since it usually utilizes hydrogen-donating solvent or atmosphere (*e.g.,* methanol, ethanol) as the substitute of water to stabilize the active intermediates [14, 181]. On the other hand, in-situ hydrogen can achieve the hydrogenolysis depolymerization of raw material [176]. As delineated in Fig. 7, the depolymerization mechanism of commercial alkali lignin solvent liquefaction in ethanol and formic acid was illustrated, mainly including hydrogenation, hydrogenolysis, demethoxylation, alkylation, reduction/dealkylation, and dehydration [176]. By this way, 36.7 wt% aromatic derivatives are obtained. Similarly, by applying solvent liquefaction with acetone, 38.04 % phenolic monomers were obtained from organosolv lignin [187]. Still, attributing to the diversity of solvents, lignin structure and catalyst option in lignin solvolysis, consensus on the general reaction mechanism and interaction has not been fully reached. As such, more works should be conducted to unravel the mechanism of solvent liquefaction.

Overall, the reaction mechanism of lignin thermal depolymerization is the result of multi-factors coupling of the temperature, time, pressure, solid loading, solvent density and type, lignin/water ratio, catalyst and lignin structure etc. So far, copious of information about reaction mechanisms of lignin thermal depolymerization has been acquired by exploring the lignin model compounds with α-O-4 and *β*-O-4 linkages. Nevertheless, the reaction mechanism about other linkage types in lignin was drawn less attention. In practice, the structure of technical lignin greatly differs with native lignin due to the modification caused by pretreatment or extraction. Technical lignin usually contains more C-C bond instead of ether bonds, indicating that more works should be devoted to these considerations. Although lignin model compounds are easier to reveal the reaction mechanism, the complexity of real lignin structure makes interaction of inter-units on material transformation also unignored versus above process factors. Ongoing work in this field should be conducted to establish a more comprehensive reaction mechanism network to further accelerate the commercialization process of lignin valorization into chemicals via thermal depolymerization.

5.4 Base-catalyzed and acid-catalyzed depolymerization

It is well-known that lignin is hardly soluble in water because of its medium-polarity. Conversely, the water solubility of lignin in alkaline medium is significantly enhanced attributing to deprotonation of phenolic OH-groups of lignin, which offers an exceptional route to produce chemicals via base-catalyzed depolymerization (BCD) of lignin [22]. The Brønsted basicity originated from the base in water can alter the electronic structure of lignin and beneficial to dissolution and depolymerization [188]. Compared with non-alkali medium, the depolymerization yield of lignin in alkaline medium can be increased by more than 4 times [189]. In general, BCD is performed under relatively harsh operating environment (> 300°C and > 200 bar), from which main depolymerization products include aromatical chemicals, char and bio-oil [190]. Commonly used base catalysts mainly include soluble base catalysts (NaOH, KOH, LiOH, K_2CO_3, etc), solid base catalysts (MgO, CaO, *etc.*) and organic N-bases catalysts [191-193]. Alkaline property and reaction parameters are crucial factors to determine the product's yield and distribution. Comparing with weak base (*e.g.*, LiOH), strong base (*e.g.*, NaOH) is more favoured to form the products like bio-oil because of the stronger polarization force on the ether bond [188, 192]. Meanwhile, the strong base can decrease the char formation and maintain the reactivity of the phenolic compounds [194]. Also, the concentration of basic solution (*e.g.*, NaOH) is proportional to the formation of lignin monomeric [195]. Notably, when applying water as solvent, low concentration of base hardly depolymerize lignin [196]. Thus, organic solvents like ethanol step into the researcher's sight as it is conducive to the solvolysis of ether linkages [197]. But a main drawback of using organic solvents is the formation of condensed structure between organic solvents with the lignin substrate [198].

During BCD process, aryl-alkyl ether bonds including *β*-O-4 are predominantly cleaved due to their vulnerability [161]. Typical reaction mechanisms on the most prevalent lignin linkage type, the *β*-O-4 motif, are illustrated in Fig. 8 [199]. Notably, in the process of ether bond cleavage to form monomers, quinone methide is considered as a crucial intermediate because of the trend of aromaticity restoration [22]. It is readily to react with nucleophile, thus resulting in the repolymerization by creating C-C bonds. On the other hand, it can be converted into enol-ether structure A accompanied by the removal of a formaldehyde [161, 200]. But the breakage of ether linkages in A is difficult to occur in base-catalyzed lignin depolymerization [200]. In addition to the *β*-O-4, the reaction mechanism of *α*-O-4 bonds cleavage is also dissected [38, 191]. The free alcoholic hydroxyl on the *p*-carbon atom or phenolic hydroxyl in the *para*-position of the *α*-aryl ether group first is converted into quinone methide intermediate. Driven by alkaline catalysis, the intermediate is further converted into vinyl ether. Meanwhile, in the presence of nucleophile like hydrogen sulfide, the intermediate can also be converted into guaiacol and coniferyl alcohol.

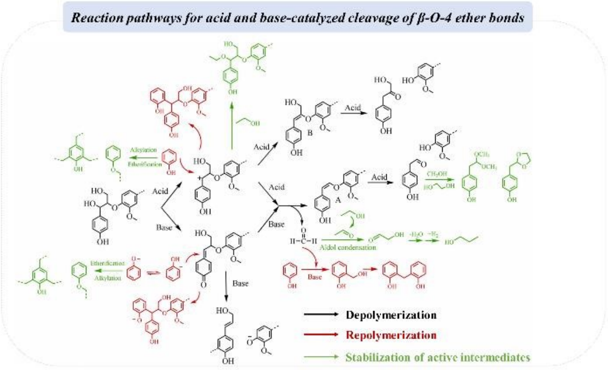

Fig. 8 Reaction pathways of cleavage of *β*-O-4 ether bonds in acid and base-catalyzed depolymerization. Reused from [199], with permission. Copyright 2023, Elsevier.

By contrast, acid-catalyzed lignin depolymerization provides a pathway to achieve lignin valorization under milder conditions (100°C) [201]. Currently, used acid mainly includes hydrochloric acid, sulfuric acid, phosphoric acid, formic acid, *p*-toluene sulphuric acid and solid acid [201-204]. Delineated reaction pathway for cleavage of *β*-O-4 ether bonds in acid-catalyzed depolymerization is delineated in Fig. 8 [199]. Concisely, the OH-group on the *α*-position is firstly removed to create a benzylic carbanion. Then, there are two pathways for further transformation. On the one hand, the benzylic carbanion can be converted into A accompanied by the removal of a formaldehyde. Alternatively, it can also be converted into structure B without removing formaldehyde. Finally, C2-aldehyde and C3-ketone substituted phenolics are created by the breakages of ether linkages in A and B.

Indeed, regardless base-catalyzed of acid-catalyzed lignin depolymerization, the repolymerization reaction is unavoidable (Fig. 8) [199]. In acid-catalyzed lignin depolymerization, due to the higher electron density the ortho- and para- positions of phenyl ring and phenolic hydroxyl in monomers, it is easy to react with benzylic carbanion to cause repolymerization [205, 206]. Ideally, repolymerization reaction can be inhibited by alkoxylation caused by the reaction nucleophilic specie like alcohol and benzylic carbanion (Fig. 8) [199]. Analogously, quinone methide is a vital intermediate to induce the occurrence of repolymerization reaction in base-catalyzed lignin depolymerization. It is readily to occur additional reaction with an electron-rich benzene ring or phenolic hydroxyl in monomers. Additionally, hydroxymethyl group can also be formed by the reaction between formaldehyde and phenyl ring [38]. Then, hydroxymethyl group further forms a methylene bridge with another phenyl ring. Likewise, using nucleophilic specie can stabilize these intermediates to suppress the occurrence of repolymerization reaction (Fig. 8) [199].

5.5 Chemical depolymerization

Generally, chemical depolymerization of lignin can be categorized as the catalytic oxidative and reductive depolymerization, both of all can be assisted to complete by different strategies like acid/base catalytic depolymerization, electrocatalytic depolymerization, and photocatalytic depolymerization reactions [207]. In terms of lignin oxidative depolymerization, O_2 and H_2O_2 were usually used for oxidants. Correspondingly, homogeneous and heterogeneous catalysts have been widely used in catalytic oxidative depolymerization of lignin to improve product yield and selectivity. For instance, Rawat et al., obtained 12.5 wt% total monomers from molybdenum-catalyzed oxidative depolymerization of alkali lignin using heterogeneous catalyst $CeO_2(MoPO/CeO_2)$ [208]. Meanwhile, 55 wt% ethyl acetate soluble oil was acquired. Yang et al., used polyoxometalate as catalyst to highly efficient achieved the lignin depolymerization [209]. As a result, 19.4 wt% aromatic monomers were obtained. Nonetheless, in view of easier recyclability, heterogeneous catalysts are usually preferred industrially [210]. Overall, according to the reaction pathway, catalytic oxidative depolymerization is roughly divided into three types based on the difference in oxidation site: *i.e.*, side-chain linkages oxidation, phenolic hydroxyl groups and aromatic rings oxidation [211]. In detail, side-chain oxidation of lignin mainly relating to primary hydroxy (γ-OH) or secondary hydroxy (α-OH) [212, 213]. Driven by various types of catalyst, lignin fragments can be converted into phenolic aldehydes, ketones and so forth. A great benefit of side-chain oxidation is to avoid the condensation reaction resulted from the formation of carbocation by converting Cα/γ-OH into Cα/γ=O(H). Also, the BDE of β-O-4 bond is effectively reduced [211, 214]. At present, considerable works uses the pre-oxidation strategies of Cα/γ-OH group on lignin for enhancing depolymerization and preventing the formation of carbocation. When the oxidative sites occur on the phenolic hydroxyl groups or the C1-Cα bonds, lignin will be converted into benzoquinone-associated chemicals [211]. In term of lignin substrates, it can be divided into phenolic and non-phenolic lignin substrates. For phenolic substrate, the hydrogen atom in phenolic-OH is firstly abstracted by superoxo complex to create phenoxy radical. Then, *p*-quinones is formed by removing substituent groups under the attack of superoxo complex or the dioxygen on C1 site [215]. On the contrary, under the case of without phenolic-OH, phenoxy radical cannot be created. Correspondingly, alkoxo intermediate and H_2O are created. Finally, veratryl aldehyde as product is formed [216]. As for aromatic rings oxidation, it is considered as the overoxidation. Under this case, lignin is firstly depolymerized into *p*-quinone and *o*-quinone, which are further converted into aliphatic (di)carboxylic acids by ring-opening [217, 218]. Such valorization pathway may reduce the advantage of lignin as unique renewable aromatic resource. Notably, the side-chain oxidation of lignin seems to be more advantageous since it provided the chance to simultaneously achieve lignin extraction and depolymerization in a one-pot single-catalyst system. For example, Du et al. firstly obtained the 96% of the stabilized lignin by catalyzing the methoxylation of the active α-OH groups of lignin at low temperature (100 °C). Then, by elevating the temperature to 140 °C, the 74.0 % of the lignin was depolymerized and 45.9% of aromatic monomers was obtained [219]. Nonetheless, carbohydrate separation step is still required since it was degraded by oxidative catalysis under alkaline conditions. Using non-basic organic solvents to substitute alkaline aqueous may be beneficial to simultaneously acquire the high quality of carbohydrates and the production of aromatic monomers in one-step catalyst system. Luo et al. designed a novel reactor with catalyst cage and acquired 15% of phenolic products yield [220]. In such reactor, the extracted lignin and carbohydrates exist in the form of solution and solid respectively. Lignin was oxidized while the degradation of carbohydrates was prevented. Indeed, attributing to the difficulties in controllability of oxidative depolymerization, more work was concentrated on the development of specific catalysts.

Reductive depolymerization of lignin can simultaneously crack lignin and stabilize radical intermediates, which is usually performed in the presence of H_2 atmosphere (H_2 or alcohol solvent) and heterogeneous catalyst, which simultaneously accompanied by hydrogenation and hydrogenolysis [221]. During reductive depolymerization, lignin extraction is performed by breaking the ester/ether bonds in lignin-carbohydrate complexes and depolymerization is achieved via cleavage of *β*-O-4 motifs [222, 223]. Lignin fragments are stabilized by the reaction between active intermediates with hydrogen or small molecules, and thus avoiding the lignin condensation. Consequently, reductive depolymerization has the additional benefit of upgrading the depolymerization product in contrast to oxidative depolymerization. Currently, the widely used catalyst in reductive mainly included carbon-supported metal catalyst, supported metal phosphate catalysts and composite catalysts [224-226]. For example, Liu et al., acquired 41.4% of mono-phenolic compounds yield by the reductive depolymerization of Birch wood sawdust using Ru/C as catalysts. Additionally, the selective conversion of 4-propyl guaiacol and 4-propyl syringol is up to 82.8% attributing to the hydrogenation of side-chain C=C bonds [227]. Gao et al., designed a Ni loaded metal phosphates catalyst to achieve 97.25% conversion from vanillin to 2-methoxy-4-methylphenol [225]. Overall, catalyst plays a crucial role in reaction direction and products yield. Besides, hydrogen source is another crucial role in reductive depolymerization. Based on the difference on hydrogen source, reductive

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depolymerization was categorized as non-self-transfer hydrogenolysis/hydrogenation (NSTH) and self-transfer hydrogenolysis/hydrogenation (STH) [193, 228, 229]. In NSTH process, exogenous hydrogen like hydrogen gas or hydrogen-donor solvents is used to cleave the β-O-4 bond. Simultaneously, reactive intermediates are stabilized to enhance phenolic monomers yield and reduce char formation [193, 228, 229]. Nonetheless, a main drawback of NSTH is that the use of grey hydrogen originated from fossil fuels significantly increases the carbon footprint. Meanwhile, harsh condition (>200℃ and > 2Mpa) and overreaction of aromatic products will inevitably reduce the sustainability of lignin-based bioenergy utilization [38]. Conversely, STH mediated by in situ hydrogen from lignin provides a promising strategy in term of sustainability and controllability because of multiple advantages, like simplification of the separation on hydrogen-donor solvents and products, and improvement of sustainability [229]. The hydrogen in STH can be derived from CαH–OH groups, $C\gamma H_2$-OH groups, methoxy groups and C–H of the side chain on lignin [229]. Notably, endogenous hydrogen efficiency varies with groups. For example, the amounts of $C\gamma H_2$-OH is higher than CαH–OH [230]. However, the formed γ-CHO may cause condensation or decarbonylation [230]. Besides, the risk of catalyst deactivation is elevated due to the chelate between $C\gamma H_2$-OH and catalyst [231, 232]. It suggested that CαH–OH-mediated STH is easier that $C\gamma H_2$-OH-mediated STH. In conclusion, the utilization of endogenous hydrogen is conducive to enhance atom utilization and sustainability. Still, more works like the reactivity of these groups and identification between catalyst and groups needs to be conducted to tailor high-efficiency depolymerization.

Regardless of oxidative depolymerization or reductive depolymerization, the precise identification of active sites on the catalyst is especially important because the surface atoms at active sites provide the highest catalytic activity to drive the occurrence of specific chemical reactions compared to other sites. At present, common catalysts in catalytic oxidative/reductive depolymerization includes metal-based catalysts such as Ni, Ru, Pd-based catalysts, metal oxides catalysts, supported metal phosphate catalysts and composite catalysts [32, 224, 225]. The active sites have been well-revealed in specific chemical conversion, such as metal atom, Lewis acid sites (LAS) and Brønsted acid sites. Still, in terms of some catalytic depolymerization process that was assisted by other technique still need to dissect the relationship between the action of active sites and reaction mechanism. For example, in electrocatalysis -mediated oxidative/reductive depolymerization, the reported electrocatalysts mainly includes metal-, carbon-based catalysts and single-atom catalysts [29]. Despite the active sites have been well-elucidated in electrochemical process, like terraces, steps, kinks, edge and corner sites in metal-based catalyst, doped heteroatoms or carbon atom activated by doped heteroatoms in carbon-based catalyst and metal atoms in single-atom catalysts [29], but the relation of active sites and reaction mechanism in the electrocatalytically assisted oxidative/reductive depolymerization needs to be further studied, which would be conducive to guide the design of high-performance catalysts in a real lignin biorefinery, and so are other technique-mediated oxidative/reductive depolymerization process. Besides, more efforts on kinetics model development are necessary since it is conducive to shed the in-depth understanding on the reaction mechanism of lignin chemical reaction from the perspective of transport phenomena, adsorption/desorption behaviour, and surface and bulk reaction kinetics [226].

5.6 Summary

As mentioned above, numerous methods have been developed toward depolymerization of lignin into platform chemicals. Despite these methods offer a feasible strategy, the limitations of these methods should be highlighted to promote commercial application of these techniques with economically profitable and environmentally friendly. Concretely, pyrolysis of lignin is commonly used for bio-oil production. Obviously, extremely high temperature and pressure are required. Besides, due to the existence of reactive oxygenated moieties such as aldehydes, ketone, carboxylic acids, etc., bio-oil has characteristic as low energy, high viscosity and corrosiveness, and easy polymerization. Thus, its further upgrading is essential for bio-oil quality enhancement. Likewise, hydrothermal liquefaction and solvent liquefaction of lignin are also performed under harsh operating conditions. By contrast, oxidative or reductive depolymerization occurs under relatively mild conditions. However, unexpected carbon-carbon bonds are created in oxidative depolymerization because of the recondensation resulted from the uncontrollability of radical intermediates, carbocations in the C_α site of lignin substrate and quinone methide, thereby reducing the products' selectivity [229]. Conversely, recondensation of lignin fragments can be avoided by the reductive depolymerization of lignin since the radical intermediates are stabilized by various hydrogen donors like H_2 and ethanol, a type of grey hydrogen. However, the utilization of these hydrogen donors reduces the sustainability of this technique due to that they derived from fossil fuels. Additionally, the production process of grey hydrogen significantly elevated the carbon emission. Lignin self-transfer hydrogenolysis in which lignin itself is used as hydrogen donor (a type of green hydrogen) provide a promising strategy for lignin reductive depolymerization since it has the advantages of reducing energy input, enhancing operation safety, improving hydrogenolysis capacity, decreasing carbon emission and avoiding overreduction. For acid/base-catalyzed depolymerization, catalyst poisoning and separation are the main issues that need to be addressed urgently, which also accompany the other catalytic processes. In conclusion, effective solutions to these problems will make great contribution on large-scale application of these techniques, finally promoting the commercial application from the perspective of energy development and environmental protection. In addition, more works on reaction mechanism of different types of C-C bonds in various depolymerization method should be performed in future since C-C bonds account for majority in technical lignin like Kraft lignin. It is conducive to tailor-made strategies for converting lignin into chemicals.

6. Separation strategy and principle of lignin-based chemicals

A diverse of products such as aromatic monomers and oligomers can be acquired after lignin depolymerization, thereby a tailor-made strategy to recover specific product is essential in term of its commercial application. At present, the developed strategies can be categorized as in-situ separation strategy and ex-situ separation strategy (Fig. 9). Concretely, in-situ separation strategy relates the

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online separation of the products in lignin depolymerization reaction system (simultaneous occurrence of lignin depolymerization and products separation), mainly including biphasic extraction system and membrane separation. On the contrary, ex-situ separation strategies, including extraction, membrane separation, distillation, and chromatography, involves the extra separation step after lignin depolymerization. In this section, the principle of various products separation techniques and evolution of some typical cases are dissected.

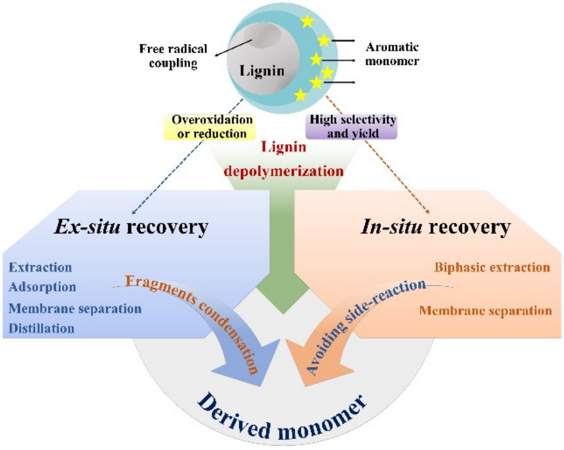

Fig. 9 Characteristic of in-situ and ex-situ separation of depolymerized products.

6.1 Ex-situ separation strategy of lignin-based chemicals

6.1.1 Extraction

Attributing to the significant difference of depolymerization products (aromatic monomers and oligomers) on polarity and molecular mass, liquid-liquid extraction provides a feasible option to recover aromatic monomers. Concisely, aromatic monomers are featured as the weak polarity and low MW, exhibiting superior solubility in weak polar solvents. Whereas, aromatic oligomers are relatively insoluble [233, 234]. Currently, used extracting agent mainly involves water, alkaline, organic solvents, chemical agent, ionic liquid, CO_2 (supercritical extraction), etc [235-242]. Separated products mainly include bio-oil, phenolic compounds and so forth [235, 239, 240]. Nonetheless, a great limitation of using single solvent as extracting agent is still the complexity of separated fraction. To tack with such bottleneck, continuous extraction with multi-steps suggested a promising option to recover various products [237, 241]. However, procedures are complicated. Alternatively, mixed solvent extraction consisting of polar and apolar solvents can achieve the separation of multiple components in one step because the polarity of the mixed solvent can be flexibly regulated by altering the volume ratio of polar to apolar solvents to match the solubility of aromatic monomers and oligomers [243]. Still, the high cost and toxicity of organic solvents are difficult to avoid. Also, acidification is unavoidable when using organic solvents to extract the products in black liquor. Undeniably, this would cause quantities of acid consumption and products loss caused by precipitation [244]. For chemical extraction, the principle is to form chemical bonds by chemical reaction of extractant and relevant components in the feed. Then, the product was further separated by other methods [245, 246]. Salting-out extraction, based on the difference of substrate solubility between the two phases (*i.e.*, solvent and salt solution), is widely used method to recover the non-distillable compounds from depolymerization products of lignin. The widely used chemical agent mainly include $CaCl_2$, $FeCl_3$ and K_2CO_3, etc [247]. This method may provide the chance to in-situ transfer the product, which is conducive to enhance the product yield. However, the additional separation step is required. Comparing with conventional liquid, supercritical fluids gained wide attention due to its controllability on gas-like and liquid-like densities [248]. Overall, CO_2-based supercritical extraction technique has the advantages of non-toxic and carbon emission reduction, but the high energy input increases the economic burden [238].

6.1.2 Adsorption

In addition to liquid-liquid extraction, solid-liquid extraction (adsorption) is also applied in the products separation [244, 249-251]. The principle of adsorption is based on the interactions between the exchange resin and products, mainly relating to van der Waals, acid-base interaction, electrical interaction, hydrogen bond, π-bond, covalent bond. These interactions result in chemical or physical adsorption [252]. Typical solid extracting agents are anion and cation exchange resins [244, 249]. They have ability to directly separate the products in alkaline solution, avoiding the acid consumption caused by acidification [244, 252]. According to the affinity for counter-ions, it can be divided into strong or weak exchangers [252]. Strong cation exchange resins-based solid-liquid extraction has been used for the separation of low molecular mass aromatic compounds from oxidized sulfite liquor, a type of material similar to black liquor [244]. But the preferred separation within the phenolic compounds cannot be achieved when using cation exchange resins. This is because that phenolic compounds with a high pKa (*e.g.*, phenol: pKa=9.9) is considered as a molecular state presented in solution and thus is difficult to separate by ion exchange [249]. Still, phenolic compounds can be slightly adsorbed due to the pore structure of the resin. Conversely, basic anion exchange resin can effectively separate the low molecular phenol derivatives from alkaline solution or black liquor while separated products are desorbed in acidic conditions [244]. Another effective option to separate phenolic monomers is nonpolar resin [253]. It can directly separate phenolic acids, aldehydes and ketones from real solution. Notably, pre-separation of HMVL is necessary considering the potential precipitation caused by the decreased pH. Also, selecting adequate desorption system is crucial for the products liberation with high purity.

6.1.3 Membrane separation

Apart from extraction, membrane separation (MS) such as UF and NF is another viable strategy to recover the depolymerized products. In membrane separation process, two distinct valuable streams can be simultaneously acquired driven by pressure [254]. Concretely, concentrated solution with great potential to produce lignin-based polymers is remained in retentate stream while permeate stream is rich in high value-added chemicals. The principle of products' membrane separation is the same as membrane separation of lignin (*i.e.*, difference between product molecular mass and membrane cut-off). In 2012, the first case of using organic solvent NF to separate the chemicals from real oxidized lignin solution was reported [255]. An advantage of using organic solvent is that it is conducive to the membrane stabilization. Also, it fits in with the existence of depolymerized products. By applying organic solvent NF, an effective separation performed for lignin oxidation product is observed, with a

<39% of rejection values for monomer and >77% of rejection values for other groups of products. In MS, the used membrane mainly includes organic with excellent mechanical, chemical and thermal stability, and ceramic membranes with life span, higher resistance to temperature and chemicals [256]. By contrast, ceramic membranes have more advantages. Notably, understanding the interactions and interplay between the permeating species (*i.e.,* solutes and solvent) and the membrane material is especially critical since it is conducive to the selective separation of depolymerized products. Based on these considerations, recently, Grignard-functionalized ceramic membrane was developed [257]. It can selectively retain individual solutes, which stems from the chemical property of the grafted groups [257]. Overall, the study on products separation by membrane technique is few. Also, the avoidance on flux decline caused by concentration polarization and pore blockage is still a great challenge.

6.1.4 Distillation

Distillation separation and chromatographic separation are also used for products separation [258-261]. In terms of petroleum refineries, it is proper to use distillation since the most compounds are volatile. Conversely, the chemicals derived from the biomass are considered as the non-volatile and the solution is typically diluted (require for water evaporation) [257]. As such, great energy input is required (30–40 kWh/m for water removal) for evaporation [257]. Another drawback is that extremely high temperature would cause the reduction of heat-sensitive substances [262]. Vacuum distillation has drawn ongoing attention because it can reduce the adverse effect on heat-sensitive substances. By applying vacuum distillation, 100% of 4-*n*-propylguaiacol (PG) and 94.5%4-*n*-propylsyringol were recovered from the catalytic hydrogenolysis solution of lignin [258]. Another method to enhance the separation efficiency of heat-sensitive substances is molecular distillation [263, 264]. In this way, light fraction, middle fraction, and heavy fractions in bio-oil were effectively separated [265]. Still, the high energy input is the barrier that hinders its commercial application.

6.2 In-situ separation strategy of lignin-based chemicals

By contrast, in-situ separation (membrane separation and biphasic extraction) is more attractive than ex-situ separation since the products can be timely separated to avoid its overoxidation or overreduction, thereby improving the final product' yield and selectivity. However, the case of membrane separation in in-situ separation is not prevalent as that in ex-situ separation, potentially attributing to the harsh environment of reaction system. Most common usage scenarios of membrane separation in in-situ separation occurs in the field of lignin electrochemical or enzyme biorefinery due to the ease of configuration of the reactor and the mildness of the reaction conditions [266-268]. In enzymatic depolymerization of lignin, the in-situ membrane separation of lignin fragments effectively prevents the repolymerization. Additionally, reaction equilibriums were altered, favoring the lignin depolymerization [268]. Still, it is well-known that membrane fouling is an omnipresent challenge in membrane applications. To mitigate this issue, a composite electrode mixer which integrated a rod electrode with a 3D-printed static mixer was developed in lignin electrochemical conversion. By this reactor, the residual lignin and products were in-situ separated. Also, the product yield was increased by 1 time [266]. Likewise, the effect of various process parameters on electrochemical membrane reactor process was analyzed by sensitivity analysis. By optimization, the aromatic product yield in the membrane reactor with cut-off of 750 Da and pore diameter of 1 nm was enhanced by 1100 time than that in in the batch reactor [267].

Conversely, biphasic extraction provides wider applicability to the separation bio-oil and aromatic monomers in the scenes with relatively high operating temperature or pressure like acidolytic oxidative and microwave depolymerization [269-271]. The basic principle of biphasic extraction is that lignin depolymerization is achieved in reactive aqueous environment followed by depolymerized products is in-situ transferred into an inert protective organic phase [269, 271]. Simple examples, attributing to the high ash content in alkaline lignin, the quality of bio-oil recovered by direct evaporation was poor. Fortunately, the developed ethyl acetate water-based biphasic extraction gave the chance to improve the bio-oil's quality due to impurities removal [270]. Besides, acidic condition is more conducive to extraction versus that in basic condition or neutral condition attributing to the change in affinity between the solutes and the extracting agent caused by ionization of solutes under various pH levels [270]. In addition to bio-oil, biphasic extraction was also applied in aromatic monomers' in-situ separation [269]. By applying biphasic extraction consisting of water and octanol in lignin oxidative depolymerization, vanillin yields was enhanced by 6 times than that in monophasic system [271]. Still, the performance of biphasic depolymerization is associated with raw material, liquid-liquid ratio, extracting agent property, temperature and so forth. More works should be performed to optimize the lignin biphasic depolymerization. Overall, the novel design of low-cost separation technique with enhanced separating power should be widely concentrated and explored.

6.3 Summary

In fact, in contrast to lignin extraction, separation and depolymerization, the work on separation of chemicals after lignin depolymerization obtained relatively less attention. However, considering the products diversity caused by low selectivity in real lignin depolymerization, its separation is one of essential step to achieve product's commercialization application. It is reported that product separation accounts for the 27.17% of total cost in catechol production by lignin depolymerization under alkaline condition, which approaches that in depolymerization process (27.83%) [12]. Obviously, no matter technical route or economic cost, the work on chemicals separation should be continuously concentrated with other subprocesses. Within these available methods, no matter in-situ or ex-situ separation techniques, they have their own advantages and limitations. Simply, in-situ separation technique poses the ability to regulate product selectivity or yield than ex-situ technique. Nonetheless, the in-situ separation techniques like MST may be limited in term of applicability due to the harsh reaction environment. Overall, in order to precisely tailor the strategy, some enlightenment about solvent option can be obtained from the relevant mechanism of lignin solvent separation. Additionally, the economic analysis or LCA should be incorporated into the study of derived new strategy.

7. Typical chemicals from lignin and commercial application case

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Overall, the most common uses of lignin-based compounds mainly include jet fuel, antioxidant material like lignin-derived polyphenols, carbon material, aromatic compounds like phenol, aniline and acid [272-274]. In contrast to cellulose (17.5 MJ/kg), lignin posed a higher energy content (22.2–28.5 MJ/kg) [275]. As such, lignin is considered as the most ideal candidate to produce biomass-based jet fuel, which can simultaneously reduce the adverse impact on environment. Notably, biomass-based jet fuel cannot completely substitute the traditional fuel since the structure of biomass is lack of aromatic and cycloalkane hydrocarbons [276]. Thus, the mixed use of biomass-derived fuels and traditional fuels is essential in terms of quality and performance standard. It was reported that the price of lignin-based jet fuel is 1300–6400 USD/ton in 1–50% mixing rate with fossil jet fuel [277]. Attributing to the diversity of lignin-based compounds, they are also used to produce antioxidant material and carbon fibers, which strongly relies on the lignin property. Generally, high *M*w lignin can be used as the raw material of carbon fibers synthesis attributing to its high mechanical properties [96, 103]. In terms of low *M*w lignin, it is featured as the abundant reactive functional groups, which can effectively scavenge active free radicals [99-102]. Up to now, the most studies about lignin valorization still concentrated on the aromatic chemicals production. Indeed, complexity of lignin structure and diversity of strategies endow lignin with great ability to produce various aromatic chemicals. Still, benzene, toluene and xylene are recognized as the most ideal raw aromatic material since they are the vital fundament to produce other chemicals [210], which accounts for 60% of the entire aromatic compounds market and 24% of global petrochemical market [273]. It was reported that the global production of these three kinds material by petroleum in 2011 achieved 36, 10, and 35 Mt/year, respectively [210]. Undoubtedly, it is exciting to use lignin as the replacement of petroleum to produce these materials. However, the deoxidation and separation of monomers extremely increased the cost. Commercial application of such production system is rare. Additionally, lignin-based hydrogels, and electrodes etc., were also widely studied. More detailed information about the application of lignin-based compounds can be found in recent review [272].

The commercial application of lignin production is available. At present, the yield of technical lignin on a commercial scale is 1.65 Mt/y, 79% of which as lignosulfonates and 16% of which as Kraft lignin [278]. In terms of lignosulfonate, the producer mainly contains Borregard Lignotech, Nippon Papers, Domsjö Fabriker AB and so forth, in which Borregard Lignotech was regarded as the world's largest lignosulfonate producer (with a maximum annual output of 650,000 tons) [139]. In terms of Kraft lignin from black liquor produced in the pulping industry, it was recovered by LignoBoost technology and LignoForce technology [278]. Concretely, LignoBoost technology is conducted based on the acidification of filtered black liquor [106], which is presently owned and commercialized by Valmet. While LignoForce uses an additional oxidation process to convert sulfur compounds and promotes the filtration process [279], which is developed by FPInnovations (Pointe-Claire, QC, Canada) and NORAM (Vancouver, BC, Canada) [118]. Conversely, the production of the other lignin like hydrolysis lignin and organosolv lignin is still under development [139]. Generally, the market price of lignin ultimately maintains a relatively stable level, with a price of 50 to 280 USD/MT for low purity lignin and 750 USD/MT for high purity lignin [280]. Undeniably, the production and cost advantages of lignin in such quantities pave the road to produce lignin-derived chemicals at commercial scales. Nonetheless, there are only a handful of commercial cases for lignin-derived chemicals production. Lignin-derived vanillin and phenol are two commercially available products, which was developed since 1933 and 2015, respectively [281]. Still, limiting to the challenge on scaling up the processing and economic profit, there is still a long way to go in the production of lignin-based chemicals.

8. Tech-economic evaluation

Delightfully, various types of strategies have been developed to flexibly produce a diverse of lignin-based chemicals. Still, an evaluation on tech-economic is necessary prior to commercial application of lignin-derived chemicals. Market analysis, as a vital evaluation factor, not only determines the selection of lignin valorization route and production capacity of the factory but also predicts market risks and competitiveness of the target product [282]. The global market requirements of products that can be generated via lignin biorefinery mainly include hydrocarbon fuels, high value-added chemicals and materials. On market share, chemicals account for about 16% [282]. Obviously, a great market requirement for chemicals produced from lignin was manifested. In terms of economic benefit of products derived from lignin, they have a great market potential to compete with petrochemical-derived chemicals [17]. Taking vanillin as an example, its production on global scale is estimated to be over 6000 tons/year, with 5.75% annual growth rate [283]. Next, the average net profit of vanillin is US\$0.44/kg lignin, with the net profits range of US\$0.15/kg~US\$3.39/kg lignin [282]. Strong market competitiveness and product economy endow the opportunity to produce chemicals from lignin. Also, the other high value-added chemicals also pose considerable revenue. Such diverse of products further increase the overall revenue.

Indeed, lignin valorization into chemicals is a result of multi-process that relies on delignification, lignin separation, depolymerization and products separation, the investment cost and revenue of each subprocess should be considered into tech-economic analysis. Excitingly, the pulping process can produce 50 million tons of by-products lignin per year as a feedstock for chemicals production [284], but the cost of the delignification still needs to be cautiously considered. By evaluating the delignification cost in alkaline extraction like kraft extraction, soda extraction and lignosulfonate extraction from sugarcane bagasse, the total cost including raw material, utilities, operating and capital depreciation were identified as 47.09~60.84 million US\$/year, significantly higher than that in organosolv extraction (36.21 million US\$/year) [18]. Obviously, such high cost does not consist with the economic expectations of making chemicals from lignin in paper mills. In addition to extraction cost, the extra revenue from chemical pulps should also be as the item to identify the delignification cost of alkaline extraction. In another tech-economic analysis report including pulp biomass revenue as evaluation factor, the total investment was identified as \$4,202,000 [285]. The economic benefit can be obtained in a 16.68% of return on investment (payback of 6 years) [285]. Undeniably, investment cost significantly varies attributing to the difference in process route, simulation method and evaluation factors. The cautious consideration

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of evaluation factor is crucial to reflect the real situation of delignification cost.

For lignin separation, comparing with the high cost derived from all kinds of strong acids, "LignoBoost" is a relatively low-cost weak acid (CO_2) separation process that have been commercialized in lignin separation. Typical representative company is the Valmet company, the specific workflow can be found on the company's official website. On the other hand, in view of the successful case of membrane separation in advanced treatment unit of wastewater treatment plant and cases analysis of lignin separation, it is convincing that lignin separation by membrane may also be more commercially viable than that in solvent extraction (*e.g.* high separation cost of about \$100~\$1200/hour) [286]. Nonetheless, owing the low flux and high membrane area requirement (> 100000 m^2), the membrane separation cost (annualized membrane and equipment capital costs account for \$7.64 kg) of lignin from upstream biorefining is still up to \$8.20/kg dry product, significantly higher than the product value of \$1.11/kg [287]. To cope with the high cost, a three-stage membrane system was optimized. As such, the cost of this system is only \$0.38/kg [287], eliminating the economical bottlenecks in lignin separation stage.

In terms of products, certainly, vanillin is a superior candidate of high-value market compound since it was predominantly applied in food, perfumery and pharmaceutical industries [51]. Lately, some studies of tech-economic analysis of overall process about the depolymerization production and separation of vanillin were performed. Comparing with solvent extraction and vacuum distillation, vanillin derived from oxidative depolymerization of Kraft lignin was separated by solvent extraction followed by distillation is more advantageous since it exhibited best economic returns (payback time of 6.19 years and internal rate of return of 22.63%) that are better than the payback time (6.9 years) and internal rate of return (20.34%) of petrochemical pathway [17]. This suggested that combinatory separation technique may be more suitable in balancing product yield and cost versus single separation technique. Notably, some other processes like NaOH regeneration and wastewater treatment should be also considered into economic analysis. When considering lignin depolymerization, products separation, alkali regeneration, wastewater treatment and so forth in alkaline oxidation of Kraft lignin, the return on investment was decreased to 10.1% and payback time was prolonged to 8 years [288].

Notably, the analyzed price comparison at the above did not indicate that some methods are absolutely most optimal choice since the evaluation criterion is not uniform. In addition, the commercial application of lignin valorization into chemicals is still few at current stage attributing to the imbalance on products yield/selectivity and investment cost. Although copious of tech-economic analysis have been performed to evaluate the economic feasibility of chemicals production by lignin, it is difficult to reflect the real situation of whole biorefinery process by some subprocess since the tech-economic analysis is not the several subprocess' simple sum. Importantly, due to the difference in feedstock, technical route, process unit, production scale, simulation method, evaluation factor and so forth, the economic analysis results vary. As such, an in-depth tech-economic analysis with more comprehensive evaluation factors from the perspective of the whole process of lignin biorefinery is needed in further work in pursuit of the commercial application of lignin-based chemicals production.

9. Challenge and perspective

Currently, copious of efforts have been conducted to accelerate the lignin integration into chemicals to mitigate the reliance on non-renewable carbon sources and facilitate the diffusion and cyclic utilization of renewable carbon sources. Regrettably, the successful commercialization case is still relatively rare due to the imbalance on product's value and economic input. Lignin biorefinery is a multi-process involving delignification, lignin separation, depolymerization and products separation subprocess, of which each subprocesses understandably has a profound effect on final product yield and economic benefit. As such, the right configurations and integration implementation of subprocess determine the efficiency and cost of lignin biorefinery. Also, an in-depth understanding of lignin structure formation and metabolic pathway on gene level is vital to directionally regulate the product's selectivity and yield. Typically, widely reported lignin is G/S type, which is heterogeneous attributing to the formation of multiple subunits and linkages [13, 40]. Such feature causes complexity of reaction. Also, the instability of β-O-4 bonds of natural lignin in acid or alkaline condition accelerates the C-C bond formation and further hinder the efficiency of lignin conversion [40, 44]. Conversely, C-type lignin, consisting of simplex caffeyl alcohol subunits with benzodioxane as the dominant linkages, has the advantages of homogeneity and acid resistance [40], and it is conducive to maintain the structural integrity in lignin extraction process, with a similar bond dissociation enthalpy to G/S-type lignin (56.5 kcal/mol for C$_{\alpha}$-O and 63.4 kcal/mol for C$_{\beta}$-O) [289]. At present, the relevant study about the biosynthesis of caffeyl alcohol and its subsequently oxidative depolymerization has been reported [40]. Such evidence gives the enlightenment on regulating the expression of C-type lignin by gene engineering. Notably, gene engineering regulation of lignin should be established under the premise of fully understanding lignin biosynthesis pathway.

Despite considerable advance has been performed in basic research of various biorefinery subprocesses, there is a need for further breakthroughs, as elucidated in the summary of each chapter. Also, the grand blueprint for the commercial application of lignin was more depicted on the basic of model compounds. However, it is not equal to real raw lignin biorefinery in terms of efficiency and economy. Attributing to the great differences between real lignin and model compounds on structural complexity, solubility, viscosity, the interaction between liquid and reactor or catalyst, fluid properties and motion state and so forth, the mixed empirical results from laboratory available to date should be clarified. But it is undeniable that these works on model compounds provided an in-depth understanding on mechanisms such as reaction course and electron transfer mechanism, which are the fundamental of strategy development of real lignin biorefinery. Notably, kinetics and thermodynamics analysis are crucial in efficiency and selectivity of lignin biorefinery. Concisely, thermodynamics can dissect the possibility and direction of the reaction occurrence, which is helpful to regulate lignin product's selectivity such as hydrodeoxygenation (*e.g.*, hydrogenation of benzene ring and cleavage of methoxy group). Likewise, kinetics is indispensable in understanding reaction mechanism on molecular level, which is conducive to optimize reaction process. As such, kinetics and thermodynamics analysis should be further promoted in

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some fields like enzyme- and (photo) electro-based lignin biorefinery process.

The second-generation platforms have a high net energy balance (*e.g.*, a net of 600 GJ/ha/yr for lignocellulosic biomass into ethanol), an index to describe the economic and environmental sustainability of bio-energy platform [290]. Still, the specific sustainability criteria and economic cost should be addressed to identify whether lignin-based chemicals production brings genuine economic and environmental benefits versus their traditional rivals [291] (economic analysis is seen in section 7). Life cycle assessment (LCA) is a strong tool to evaluate the environmental effect for a product from resource development to end-of-life. Comparing with the fossil-based production method, adipic acid production from lignin can reduce the greenhouse gas emissions (GHG) of 62%~78% [292]. Analogously, the global warming potential and fossil fuel depletion of producing catechol from lignin can be decreased by 2% and 59% [293]. By integrating LCA with green design metrics, the processing performance and sustainability can be greatly enhanced [294]. Notably, catalyst may be a vital role in lignin biorefinery in term of performance and GHG emission. Noble metals with high catalytic activity and cost such as Ru and Pt have been studied. However, the high GHG emission in mining and purification of these elements should be carefully considered, like Pt (12.5 t CO_2/kg). Conversely, low-cost no-noble metal presented a lower GHG emission (<10 kg CO_2/kg), suggesting a promising pathway on GHG emission mitigation and economic viability. Thus, more works should be performed in high-performance non-noble-based catalyst development. Apart from the environmental impact and cost/activity, the mechanism on alteration of catalyst stability caused by loss of active components, catalyst agglomeration or dissolution and catalyst blockage should be explored to regulate catalyst behavior. Further work in catalyst exploitation should be devoted to the establishment of connection among cost, activity, stability and GHG emission.

Although the negative carbon emission reduction technology based on biomass energy with carbon capture and storage is considered as the promising technique to achieve the core target of the Paris Agreement and develop renewable energy, the start-up time of the negative carbon emission reduction technology is very crucial since climate change would significantly negatively affect the bioenergy emission reduction potential [295]. Ideally, global warming will reach 1.7°C in 2200 when bioenergy is initiated in 2060. However, the energy crops and food yield will be greatly reduced due to the climate warming from continuously carbon emission of traditional fossil fuel. As such, global warming increases from 1.7°C to 3.7°C in 2200, with the same start-up time with ideal situation. Also, the average per capita calory for food is decreased from 2.1 Mcal/day to 1.5 Mcal/day [295]. This suggested that delayed implementation of CO_2 emissions alleviation by bioenergy not only causes the declining ability in GHG mitigation but also increases the risk of food crisis. Overall, within the allowable scope of economic feasibility and environmental impact, lignin biorefinery should be put on industrialization as soon as possible by the right configurations and integration implementation of subprocess and selecting proper site (*e.g.*, black liquor for raw material supplying or waste gas CO_2 for lignin separation). Meanwhile, in term of biorefinery concept, the full utilization of biomass components for other application should also be a notable research effort. To further promote technical development and accelerate the large-scale popularization of bioenergy technology in a short time, various scales of demonstration project should be established to exert leading role. It is worthy mentioned that it should be very prudent to apply lignin from some extraction process such as black liquor to generate high-value products involving the biological chain because heavy metal may incorporate into structure of chemicals. Consequently, the quality detection and quality supervision are especially crucial in terms of security rather than simple pursuit on quantity of chemicals production. Meanwhile, timely user feedback survey is also crucial in terms of user demand, market variation and technical route adjustment. In conclusion, to minimize the negative effect of climate warming on bioenergy carbon emission potential (realization of Paris agreement) and food production capacity, considerable efforts need to be performed to popularize the lignin-based chemicals production process in a short time.

10. Conclusion

This review offers an in-depth mechanism dissection on lignin biosynthesis pathway and biorefinery subprocesses as well as analysis on tech-economic viability. In term of commercialization application, numerous efforts still need to be performed in the gene engineering regulation and right configurations and integration implementation of subprocess to promote the efficiency and economic benefit of whole process. Such information on mechanism understanding and technical feature analyzed by this review gives the enlightenment and reference on novel integration strategy development that fully realize the complementary advantages among subprocesses. Notably, the start-up time of lignin-based chemicals production on commercialization popularization is crucial since the yield reduction and agricultural land demand competition of energy crops and food caused by climate warming will reduce the carbon emission mitigation capacity and increase global food risk. Overall, the early start-up of commercial utilization of lignin is imminent when bioenergy is relied as the substitute of conventional fossil fuels with insufficient reserves.

Author Contributions

Rui Hu: Data curation, Investigation, Validation and Writing - Original draft. **Jiahui Zhan**: Investigation and Validation. **Yuying Zhao**: Investigation. **Xinyi Xu**: Investigation. **Gang Luo**: Validation and Writing – review & editing. **Jiajun Fan**: Writing - Review & Editing. **James H. Clark**: Writing - Review & Editing. **Shicheng Zhang**: Conceptualization, Supervision, Validation, Resources, Project administration, Writing - Review & Editing.

Conflicts of interest

There are no conflicts to declare.

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