

Process intensification strategies for lignin valorization

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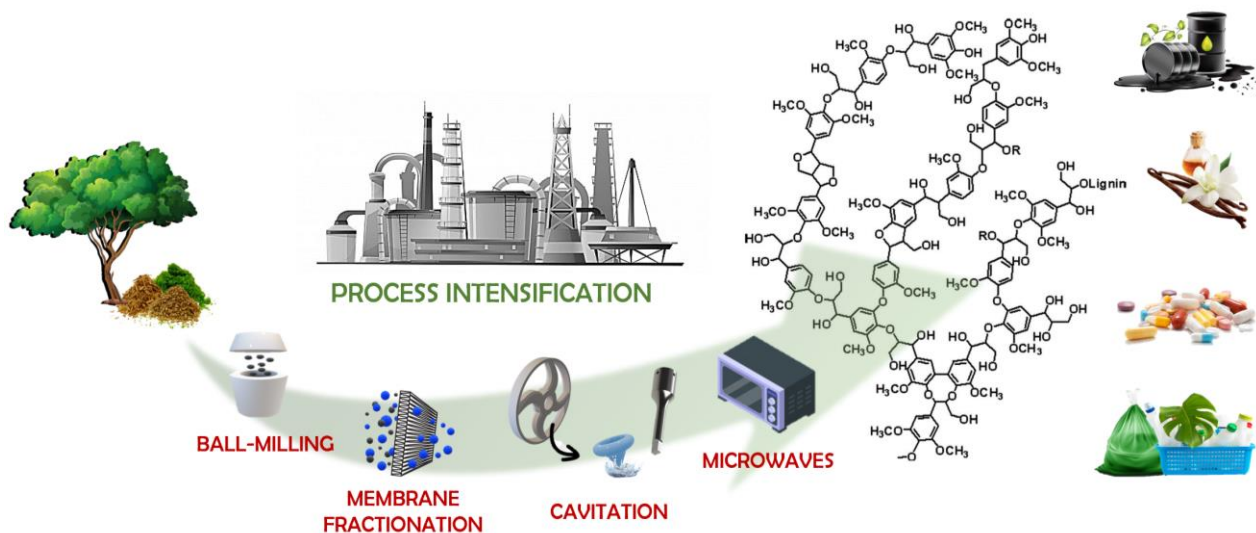
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# 1 Process intensification strategies for lignin valorization



2

3 **Keywords:** lignin, microwave, hydrodynamic cavitation, ultrasound, membrane separation

## 4 Abstract

5 Nowadays, the increasing concern about the declining fossil fuel reserves and the environmental impact  
6 derived from their use has put considerable interest in lignocellulose exploitation as a renewable source of  
7 biofuels and biomaterials, according to the biorefinery concept.

8 Several processes and technologies have been extensively studied in order to optimize biomass treatments  
9 aiming to enhance the recovery of its main products: cellulose, hemicelluloses and lignin. Lignin is, in fact,  
10 considered a valid substitute to petroleum as a source of aromatics, thanks to its abundance in nature. However,  
11 its complex and highly resistant structure limits its further applications, therefore, lignin upgrading is  
12 considered extremely challenging: various processes have been developed in recent years, but their feasibility  
13 at industrial scale still represents a bottleneck.

14 Recently, process intensification has gained considerable attention in the design of sustainable procedures for  
15 lignin valorization. In particular, non-conventional technologies such as Ball milling, Ultrasounds (US) and  
16 Microwaves (MW) have recently shown promising results in biomass exploitation, thanks to their ability in

17 generating specific high-energy microenvironments which could enhance process efficiency:  
 18 mechanochemical and US activation have been mostly applied to biomass pre-treatment, in order to separate  
 19 its components and enhance lignin extraction yield, while MW have been exploited as a means for lignin  
 20 depolymerization, achieving higher yields of aromatics in milder reaction conditions. However further efforts  
 21 should be done to improve profitability through new processes, aiming to reduce the cost associated to bio-  
 22 derived products.

23 In the present review, recent approaches to lignin valorization are discussed, focusing on new alternative  
 24 methodologies for process intensification, besides their challenges and feasibility at industrial scale.

## 25 1. Introduction

26 The decline of fossil resources, the rising cost of fuel energy and the environmental concerns have prompted  
 27 the development of sustainable technologies to produce renewable energy and chemicals. In this context, the  
 28 exploitation of lignocellulosic biomass as a renewable resource has gained increasing interest: lignocellulose,  
 29 in fact, is the primary component of plants, and, thus, it is the most abundant renewable resource on Earth.  
 30 [1,2] It is mainly composed of cellulose (40-50%), hemicellulose (15-20%) and lignin (15-25%), with a small  
 31 part of other extractable components such as water, proteins and minor compounds.[3] The composition of  
 32 various lignocellulosic feedstocks is illustrated in Table 1

Feedstock	Composition (% dry wt)			References
	Cellulose	Hemicellulose	Lignin	
<b>Bamboo</b>	36-43	18-20	23	[4]
<b>Corn stover</b>	35.1-39.5	20.7-24.6	11.0-19.1	[5]
<b>Cotton</b>	85-95	5-15	0	[6]
<b>Cotton stalk</b>	31	11	30	[7]
<b>Eucalyptus</b>	45-51	11-18	29	[4,8]
<b>Rice straw</b>	29.2-34.7	23-25.9	17-19	[9]
<b>Wheat straw</b>	35-39	22-30	12-16	[9]
<b>Grasses</b>	25-40	25-50	10-30	[10]
<b>Sugarcane bagasse</b>	25-45	28-32	15-25	[4,8]
<b>Pine</b>	42-29	13-25	23-29	[8]

<b>Poplar wood</b>	45-51	25-28	10-21	[11]
<b>Olive tree</b>	25.2	15.8	19.1	[12]
<b>Oat straw</b>	31-35	20-26	10-15	[13]
<b>Nut shell</b>	25-30	22-28	30-40	[14]

**Table 1:** Composition of representative lignocellulosic feedstocks.

33

34 In last decades, significant technological advancements have been made for processing lignocellulosic biomass  
 35 since the valorization of its principal components could offer a cheaper way to produce biofuels and chemicals.  
 36 Indeed, cellulose and hemicellulose fractions are a potential source of fermentable sugars and value-added  
 37 products, while lignin is a source of aromatic compounds. However, due to lignocellulose complex and highly  
 38 resistant structure, its treatments usually require harsh condition, which is the reason why the design of cost-  
 39 effective processes is necessary. Furthermore, the understanding of the complex structure of lignocellulose is  
 40 fundamental for a suitable valorization. Moreover, for a sustainable global development, the exploitation of  
 41 biomasses for the large-scale production of chemicals is very attractive. In fact, biomass plays an important  
 42 role in reducing greenhouse gas emissions, since CO<sub>2</sub> derived from its wastes would originally have been  
 43 absorbed during plant growth.[15]

44 For these reasons, recently, process intensification (PI) has received considerable attention as a strategy to  
 45 enhance process efficiency and sustainability by reducing energy consumption, volumes handled and waste,  
 46 while increasing productivity and safety in a simplified cost-effective process.[16] In this context, enabling  
 47 technologies based on microwaves (MW), ultrasound (US) and mechanochemical activation play a central role  
 48 in PI. In particular, US and ball mills, thanks to the generation of high-energy microenvironments, can strongly  
 49 affect biomass structure enhancing mass transfer, while MW can promote biomass conversion efficiently, by  
 50 prompting heat transfer. As a consequence, US and ball mills are typically applied in biomass pretreatment  
 51 rather than conversion reaction, where MW reactor can find wide applications. Therefore, the design of  
 52 sustainable and efficient processes for the valorization of lignin fraction could be addressed by enabling  
 53 technologies. Despite the potential of mechanochemical and ultrasound activation in biomass conversion, these  
 54 processes, as well as hydrodynamic cavitation, have been mostly applied to biomass pre-treatment, with the  
 55 aim of separating its components and enhance the lignin extraction yields. Furthermore, the intrinsic efficiency  
 56 for downstream separations of membrane technology, makes it a good candidate for intensifying the

57 fractionation of extracted lignin, in order to recover more uniform fractions for further valorization. Microwave  
58 technology, on the other hand, when used for biomass pretreatment and lignin recovery, afforded chemical  
59 modified and deconstructed lignin; for this reason, it could be more suitably exploited as an efficient tool for  
60 lignin depolymerization.

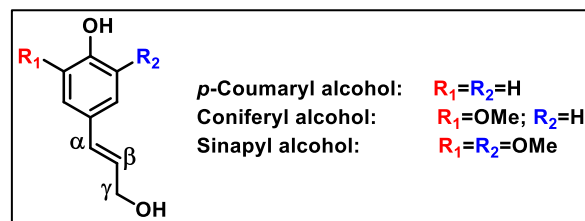
61 The aim of this review is to provide an overview of the most recent applications of non-conventional  
62 technologies for the PI of lignin extraction and conversion into high added value products, in order to highlight  
63 the advantages and the potential scalability of these technologies, compared to conventional procedures.

## 64 1.1 Lignin structure

65 Lignin is one of the main constituents of lignocellulosic biomass (15–30 % by weight) and the most abundant  
66 source of aromatic molecules in nature. [17] It consists of a highly complex structure interconnected with  
67 cellulose and hemicellulose through covalent and non-covalent bonds. [18] Despite its abundance, lignin  
68 conversion has received less attention compared to cellulose and hemicellulose in the biorefinery processes  
69 due to the challenges of converting it into high value-added products. The reason lies in the high resistance to  
70 biological and enzymatic degradation due to complex chemical linkages, that prevents plants from insects and  
71 microbial attack. In fact, lignin from bioethanol and paper pulp industry is traditionally seen as a by-product  
72 and mainly recycled as fuel for energy production. [19] However, the valorization of lignin has recently gained  
73 significant interest because it provides opportunities for different value-added applications. Furthermore,  
74 lignin can be converted into several profitable commodities, such as fuel and phenolic compounds. [17]

75 Lignin is a cross-linked amorphous hydrophobic polymer with a very complex structure which significantly  
76 varies depending on the plant species and the isolation process. Indeed, unlike cellulose and hemicellulose,  
77 lignin presents diverse monomer units and linkages (more than 400 bonding patterns are known) making it  
78 highly recalcitrant to depolymerization. Additionally, lignin weight can vary between 5 and 100 KDa within  
79 an isolated lignin. The main units are phenylpropene monomers (monolignols): trans-p-coumaryl alcohol (H-  
80 unit), trans-coniferyl alcohol (G-unit) and trans-sinapyl alcohol (S-unit) (Figure 1),[20] containing zero, one,  
81 and two methoxy groups, respectively. The ratio between these primary monomer units varies among different  
82 plants and species: coniferyl alcohol is abundant in softwood lignin (90-95%) while hardwood lignin contains  
83 both coniferyl and sinapyl alcohols and all the three monolignols are present in grass lignin.[21] Moreover,

84 lignin content in biomass decreases with the following order: softwood > hardwood > grass. Lignin  
85 monolignols are inter-linked through ether and C-C bonds, such as  $\beta$ -O-4,  $\alpha$ -O-4, and 4-O-5, as well as C-C  
86 bonds such as  $\beta$ -1,  $\beta$ -5, 5-5', and  $\beta$ - $\beta$  (Figure 2).[17] In lignin polymeric structure different functional groups  
87 are present including methoxyl, hydroxyl, benzyl alcohol, benzyl ether and carbonyl groups, which outcome  
88 in different reactivity. The proportion of these linkages and specific functional groups are highly dependent on  
89 the lignin sources and isolation methods.



90

91

Figure 1: Building block monolignols of lignin.

92 The  $\beta$ -O-4-aryl ether bond is the most abundant, representing approximately 50% of all the linkages in native  
93 lignin.[22] Consequently, the effective cleavage of this specific bonds is crucial for lignin  
94 decomposition.[23,24] However, due to the presence of various functional groups, the proportions of these  
95 linkages are different and related to the vegetal species of origin. For instance,  $\beta$ -O-4 linkages are more  
96 abundant in hardwood lignin compared to softwood, making the valorization of this type of lignin highly  
97 challenging.[25] Furthermore, technical lignins, which are isolated from biomass after several treatments,  
98 highly differ from native lignin. Their structures are related to the isolation method and usually present higher  
99 C-C linkages, a broad molecular weight distribution and some contaminations such as ashes and sulfur, which  
100 make technical lignins difficult to depolymerize.[26] The most common technical lignins (Lignosulphonates,  
101 Kraft lignin, Soda lignin and Organosolv) derive from wood pulping and have been extensively studied for  
102 lignin valorization. Hence, the variety in both monomer content and chemical bonds makes the determination  
103 of the exact chemical structure of isolated lignin extremely difficult. Additionally, for an industrial general  
104 protocol of lignin conversion into fuels and chemicals, lignin structural variability should be carefully  
105 addressed within different issues such as depolymerization, re-condensation reactions and product separations.

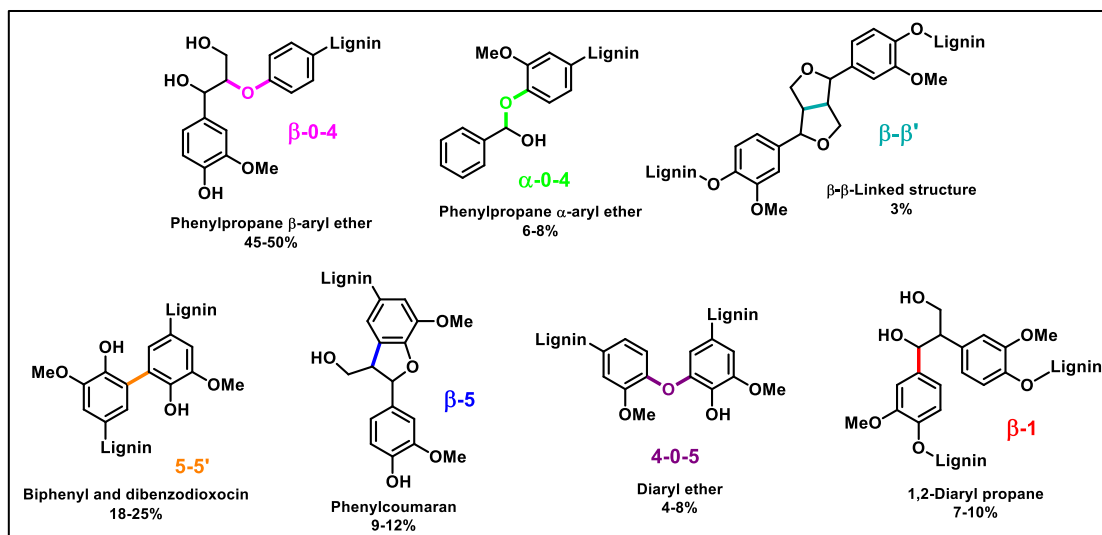


Figure 2: Typical lignin interunit linkages

## 2. Lignocellulose Pretreatment

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107

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109 Pretreatment is a crucial process step for the biomass conversion into high added value products. It involves

110 the alteration and solubilization of lignocellulosic biomass aiming to achieve cellulose, hemicellulose and

111 lignin conversion rapidly and easily, with greater yields. [27,28] Hence, an efficient separation of the main

112 components from lignocellulosic biomass is a desirable condition in lignin valorization. Although several

113 methods have been developed, the effective fractionation of biomass into its three main constituents is still

114 challenging. In fact, it is required to deconstruct cell walls and isolate its components, without drastically

115 modifying their native structure, thus aiming to simplify the subsequent conversion into valuable products

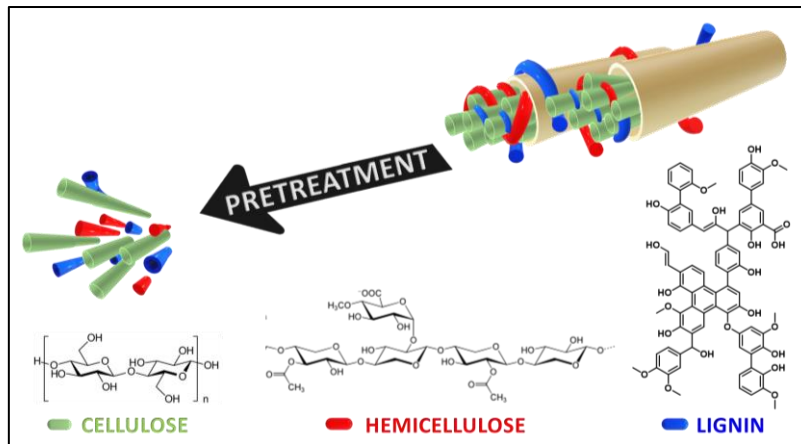
116 (Figure 3). [29] Furthermore, the choice of the optimal pretreatment protocol and conditions highly depends

117 on the feedstocks and the economic and environmental impact. The main issue still remains the removal of

118 lignin, which is highly resistant to solubilization, and which inhibits the subsequent hydrolysis of cellulose and

119 hemicellulose. Besides the necessity of its removal, delignification is a key step, as lignin can be recovered for

120 further applications with potential high added value.



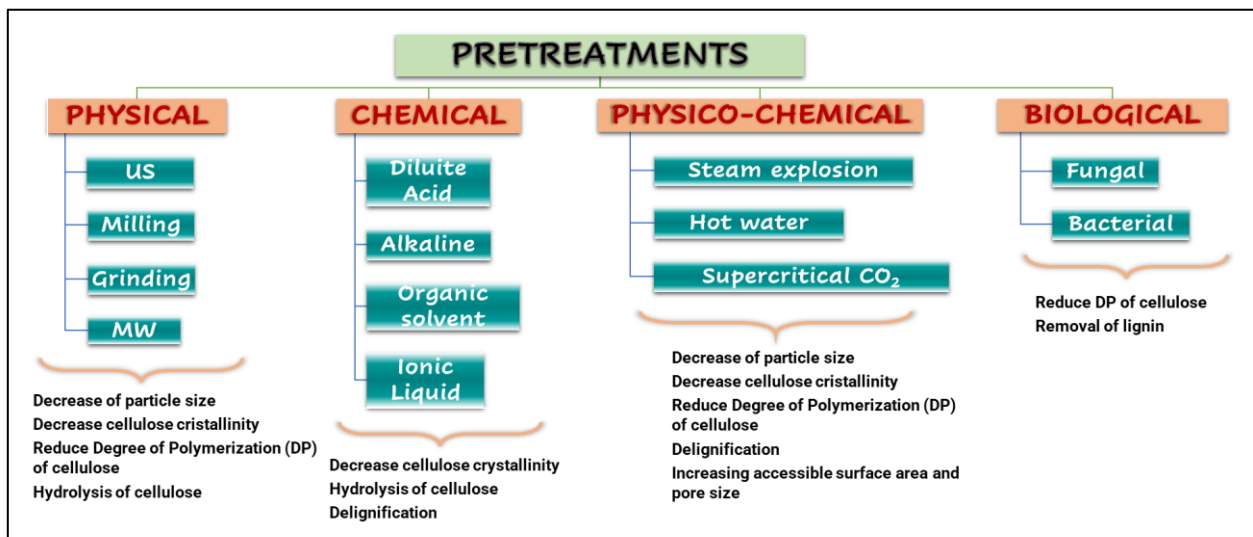
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Figure 3: Pretreatment effect on lignocellulosic biomass

123 Other factors such as lignin content, cellulose crystallinity and size of the biomass particles are also crucial  
 124 factors to consider in order to overcome lignocellulose recalcitrance. Thereby, pretreatment processes should  
 125 maximize biomass delignification and depolymerize hemicellulose by enhancing solvent diffusion; moreover,  
 126 it should reduce cellulose crystallinity and isolate uncondensed lignin, avoiding the formation of degradation  
 127 products.

128 Pretreatment methods include physical, chemical and biological processes, or a combination of them (Figure  
 129 4).



130

131

Figure 4: Various pretreatment processes of lignocellulosic biomass.

132 Biological pre-treatments are based on the use of lignin-degrading enzymes and microorganisms such as fungi  
 133 and bacteria for partial delignification of lignocellulosic materials. However, the biological approach is often



134 criticized because of the slowness of the process and the significant costs of enzymes. In chemical pre-  
135 treatments, the use of alkali, acids or, more recently, ionic liquids is required for the alteration of lignocellulosic  
136 biomass structure, thus, these methods may not be advantageous from a sustainability perspective. Physical  
137 pretreatments are used to enhance biomass deconstruction and solubilization; the major drawback is the high  
138 energy input required. Since each pre-treatment procedure reports some limitations such as the use of toxic  
139 chemicals, prolonged treatment times, elevated temperatures and pressures and high energy input, it is crucial  
140 to develop efficient and cost-effective procedures for the intensification of biomass pretreatment. [29,30]

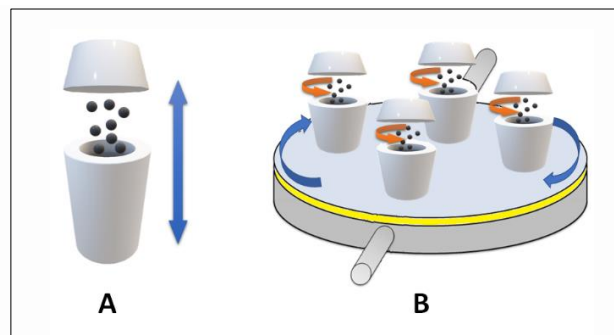
141 In the last decades, enabling technologies such as milling, MW irradiation and US have been intensively  
142 exploited as more efficient alternatives to the traditional biomass pretreatment methods. Milling reduces  
143 biomass particle size and is typically applied prior to other pretreatment methods to improve feedstock  
144 handling. Moreover, it allows the separation of biomass constituents into different fractions by the rupture of  
145 the cell wall, reduces cellulose crystallinity and decreases particles size. Cavitation, generated by US or in the  
146 form of hydrodynamic cavitation (HC), also offers a promising intensification of biomass pretreatment; it  
147 enhances solvent penetration into lignocellulose walls, improving the mass transfer of the following extraction  
148 processes. [31] Though these processes usually require high energy input, they can provide milder conditions  
149 and a reduced amount of solvents compared to conventional fractionation methods. In fact, the energy required  
150 for pretreatment highly depends on the final particle size and the crystallinity reduction of the feedstock.  
151 However, usually the pretreatment step requires more energy than the energy content available in the biomass,  
152 thus making these methods still expensive for a full-scale process.[32]Therefore, the choice of a specific  
153 pretreatment method should consider all these aspects in order to guarantee an efficient and cost-effective  
154 process in biomass valorization.

## 155 2.1 Ball milling pretreatment of lignocellulosic biomass

156 Size reduction is a key point for the valorization of biomass into energy and chemicals. In fact, the  
157 surface/volume ratio increases within the accessible area of constituents and, therefore, enhances the  
158 consequent conversion rate. Moreover, it reduces the mass and heat transfer, limiting the required energy, and  
159 facilitates the storage. [27,33]

160 Due to the heterogeneous structure of lignocellulosic biomass, usually several steps are required in order to  
161 reduce the particles size. First, it is necessary to reduce the volume of lignocellulosic material, usually by  
162 cutting biomass from meters to centimeters. Then, an intermediate milling reduces particle size from cm to  
163 mm and lastly, fine and ultra-fine milling reduce the size from mm to 20-500  $\mu\text{m}$ . Smaller sizes requires wet  
164 grinding with a consequent higher energy consumption.

165 Several types of mills have been used to fragment lignocellulosic biomass: knife mill, hammer mill, planetary  
166 and vibrant ball mill, which consist of a rotor driving different tools.[34] The most common mills in laboratory  
167 are vibrant and planetary ball mills. The motion of these instruments lead biomass to the collision with balls  
168 and walls of the vessel. This generates high localized energy able to crush materials into smaller dimensions.  
169 In vibrant ball mills, a rapid sideward movement leads balls inside the vessel to impact against the walls and  
170 its content. On the other side, planetary mills describe a circular movement while the vessels simultaneously  
171 and rapidly rotate in a counter direction, mimicking planets movement. As described before, this motion causes  
172 friction and impact at the wall surfaces.



173

174

*Figure 5: Vibrant mill (A) and planetary mill (B)*

175 High milling speed generally led to faster grinding, which may also increase the temperatures, causing  
176 formation of undesirable byproducts. However, mechanical comminution is considered one of the most  
177 expensive processing steps in converting biomass, since high energy is required.

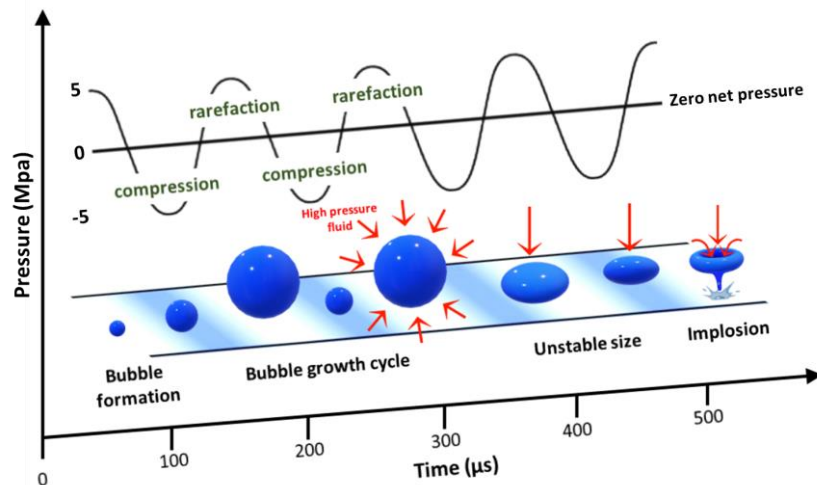
178 However, the use of milling is not limited exclusively to reduce particle size in order to enhance biomass  
179 fractionation for further applications. Björkman[35] developed a method which consist in the use of ball-mill  
180 to isolate lignin from wood. The biomass is first ball-milled and then extracted in aqueous dioxane (milled  
181 wood lignin, MWL). However, the recovery of MWL is rather low since it highly depends on the nature of the

182 biomass and milling time. When milling time increases from one day to one week, yield rises from 16% to  
183 60%, highlighting that this method is time and energy consuming, since it mainly focuses on the recovery of  
184 lignin. [36] In most cases, the advantage of using MWL lies in the fact that it is considered the most  
185 representative of lignin in its native state, since it is isolated at room temperature in the absence of any strong  
186 acids or bases. [37,38] Milling pretreatment has been proven to be an efficient method to reduce crystallinity  
187 and particle size, enhancing solvent accessibility to lignocellulose and, thus, improving also alcoholysis  
188 reactions. In this regard, recently, a ball mill pretreatment has been applied to camphorwood sawdust, aiming  
189 to obtain elevated bio-oil yield in supercritical ethanol. The reduced crystallinity and particle size increased  
190 biomass surface area (from 1.88 to 4.77 m<sup>2</sup>g<sup>-1</sup>) enhancing the solubility in ethanol. The yield of aromatic rich  
191 bio-oil increased to 59.2% compared to the 39.6% obtained without pretreatment. [39]

192 Shi et al. [40] pretreated with ball mill Softwood Unbleached Kraft Pulp (UKP) to promote its dissolution in a  
193 NaOH/urea solvent. After 60 min of milling the particle size of UKP decreased to an average diameter of 5  
194 μm, showing good distribution, and the crystal peaks of cellulose completely disappeared, indicating that the  
195 milling process could easily destroy the crystal structure of lignocellulose. Furthermore, the degree of  
196 polymerization (DP) was reduced from 1300 to 330. This promoted the subsequent solubilization of the pulp  
197 in NaOH/urea solvent. In fact, dissolved proportion of UKP increased from 25.6% to 96.0% after 60 min of  
198 milling pretreatment. However, biomass with an elevated lignin content could not dissolve in the NaOH/urea  
199 solvent due to the presence of lignin-carbohydrate complex. Ball milling treatment has been applied to  
200 investigate the effect of cellulose crystallinity, hemicellulose and lignin content on further enzymatic  
201 hydrolysis. Four fractions with different sizes (250-355 μm, 150-250 μm, 63-150 μm, and < 63 μm) were  
202 collected and then hydrolyzed. It was confirmed that monosaccharides yield increased within the decreasing  
203 of cellulose crystallinity [41] and that lignin removal greatly enhances enzymatic hydrolysis of biomass, since  
204 after delignification, even with higher cellulose crystallinity degree, high yields of glucose and pentoses were  
205 achieved, compared to the untreated samples. The energy requirement of mechanical comminution is  
206 extremely variable, as it is related to the type of instrument, initial and final particle sizes, and biomass  
207 characteristics (i.e., bulk density, processing amount, moisture content, and composition)[34].

208 **2.2 Processes assisted by cavitation**

209 Ultrasound (US) is a mechanical acoustic wave with the frequency range from roughly 10 kHz to 20 MHz  
210 generated by piezoelectric transducers which respond to an alternating current with mechanical vibrations to  
211 produce US of a certain frequency. [42,43] When the transducer is connected to a vessel filled with a solution,  
212 the mechanical vibrations of the piezoelectric material create a pressure wave through the solution (Figure 6).  
213 In a typical US-assisted process, the pressure wave through the liquid medium creates alternating regions of  
214 high pressure (compression) and low pressure (rarefaction). The rarefaction of the cycle can stretch the liquid  
215 molecules apart creating cavities also known as cavitation microbubbles. [44] These microbubbles grow to  
216 a maximum of about 4-300  $\mu\text{m}$  in diameter [44] and under the effect of ultrasonic field repetitively expand and  
217 contract. When acoustic energy has gained sufficient intensity, some microbubbles become unstable and  
218 violently collapse in several nanoseconds, generating shockwaves. [45] The microbubbles collapse is an  
219 adiabatic process, resulting in a huge amount of energy released. Therefore, local hotspots are formed that  
220 present extreme local conditions of high temperatures (ca. 5000  $^{\circ}\text{C}$ ) and high pressures (ca. 50 MPa).[46]



221

222

Figure 6: The acoustic generation of cavitation microbubbles

223 In liquid media cavitation facilitates the disintegration of solid particles, acting superficially and providing  
224 thermo-mechanical energy to the process. For instance, the instantaneous collapse of bubbles at the  
225 solid/solvent interface produces strong shockwaves and microjets at high speed ( $>100$  m/s) toward solid  
226 surfaces.[42,46] This movement of the solvent is defined as micro-convection, which intensifies the transport  
227 of fluids and solid particles compared to conventional mechanical methods. Moreover, the high-energy

228 environment generated by shockwaves is able to break chemical bonds. Cavitation can be divided into acoustic  
229 (AC) or hydrodynamic (HC), depending on its generation method. In the first case, microbubbles are generated  
230 by the pressure variation of ultrasonic waves passing through a fluid, whereas in hydrodynamic cavitation the  
231 growth and collapse of the bubbles are induced by a rapid variation in the streamlines of the fluid, which is  
232 forced through a Venturi tube or by the relative movement of a rotor/stator system.[47]



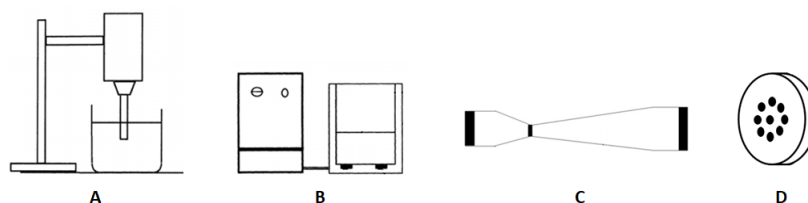
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Figure 7: Rotor stator reactor (a) and venturi (b)

### 235 2.2.1 Reactors design

236 There are several types of reactor designed for cavitation (Figure 8). [48] Ultrasonic horns are the most used  
237 reactors and typically consist of an immersion transducer which generates high-intensity region in the liquid  
238 nearby the horn. The scaling-up process of this type of US systems is not very effective since it is not possible  
239 to transmit the acoustic energy in a large volume. Furthermore, ultrasonic horns suffer from erosion at the  
240 surface, thus, they are generally used for laboratory scale investigations. In ultrasonic bath, the reactor bottom  
241 is irradiated with a single or multiple transducers. In this case, the maximum of cavitation intensity occurs just  
242 above the surface of the transducer. Thus, the area of irradiating surface can be increased in order to improve  
243 energy distribution in the reactor.



244

245

Figure 8: US immersion horn (A), US bath (B), venturi (C) and orifice plate (D)

246 HC can be generated by the flow of the liquid through an orifice plate or a valve: orifice plates can present  
247 single or multiple holes, with different diameters to ensure different cavitation intensities; furthermore, they  
248 offer more flexibility of controlling parameters such as inlet pressure, flow rate, cavitation intensity, making  
249 this system more suitable for specific applications. [49–51] The cavitation phenomena occur just after the  
250 orifice plate: when the liquid passes through the holes, due to the restricted area, the velocity increases resulting  
251 in a decreasing pressure. When the pressure goes below the medium vapor pressure, cavitation occurs. In the  
252 case of a Venturi tube, a higher velocity at the throat is generated, compared to an orifice. The Venturi  
253 configuration can be used for milder processes (typically pressure requirement between 15 and 20 bar) and  
254 physical transformations, while an orifice flow configuration is generally used for chemical reactions. In the  
255 rotor-stator system, the main energy consuming part is the spin of the rotor. Thus, the operating cost is  
256 associated to the electricity consumption by the motor, which is relatively low. Moreover, HC devices are easy  
257 to scale up compared to US reactors and several parameters, such as speed rotation, percentage of biomass and  
258 the time of treatment can be easily optimized.

### 259 2.2.2 Cavitation for biomass delignification

260 Cavitation technology has been recently applied to face the technological challenges related to the pretreatment  
261 step, necessary for the conversion of lignocellulosic biomass.[52] Indeed, current pretreatment options are  
262 expensive and require the addition of chemicals, which could be counterproductive in biofuel production,  
263 resulting in wasteful processes. For this reason, new technologies must consider processes with low  
264 environmental and economic impacts within high efficiency. US-assisted processes are influenced by  
265 frequency, duration of treatment, reactor configuration, type of biomass and solvent used. In particular, bubble  
266 cavitation is strictly connected to frequency: high frequencies (>150 kHz) do not promote active cavitation  
267 because of the insufficient duration of the ultrasonic cycle. Indeed, longer cycles are required for the growth,  
268 radial motion and collapse of the bubbles. However, short-lived bubbles can boost free-radical concentrations,  
269 leading to chemical effects, while mechano-physical effects are observed at low frequencies (20–80 kHz). The  
270 combination of these effects can modify the chemical and physical composition of lignocellulose. Indeed, the  
271 mechanoacoustic effects can alter the surface structure of the biomass, and the sonochemical production of  
272 oxidizing radicals can lead to a chemical attack of the components of lignocellulose.[52] In this frame, the

273 effect of hydrodynamic and ultrasonic cavitation on lignocellulosic biomass was reviewed according to wheat  
274 straw pretreatment.[53] The review highlighted the prevalence of physical effects of US in the delignification  
275 enhancement with low-frequency ultrasound.

276 The crucial point for a biorefinery approach relies in the enhancement of the efficiency of lignocellulose  
277 pretreatment and the following separation of the components at mild conditions. In addition, the production of  
278 undesired by-products along with lignin modification should be avoided, in view of further valorization steps.  
279 For this reason, the use of ultrasounds for biomass fractionation could be a promising technology that could  
280 be easily implemented in biorefinery processes.[54] US are mainly used for biomass pre-treatment, as an  
281 efficient tool for delignification, especially for sugar fermentation to biofuels. However, the so-extracted lignin  
282 could find higher added value applications than simple heat generation by burning or pelletizing, as the  
283 structure of lignin remains quite unchanged after US treatment.

284 In this context, US-assisted technology has been used for the pre-treatment of wheat straw (0.5M NaOH in  
285 60% aqueous methanol) and compared with conventional fractionation. [55] US were applied for a time range  
286 of 5 to 35 minutes, obtaining the solubilization of 67.4% to 78.5% of the original lignin, whereas 61.0% of  
287 lignin solubilization was obtained at 60°C for 2.5 h without sonication. Moreover, US-isolated lignin showed  
288 slightly lower molecular weights and no significant differences with respect to the native lignin of wheat straw,  
289 confirming the efficiency of the US-assisted lignin extraction procedures.

290 The same research group performed a similar experiment using 0.5M KOH to extract lignin, comparing  
291 conventional and US-assisted procedures. [56] Even in this case, higher lignin yield in shorter times was  
292 obtained under US (from 43.9% to 49.1% when US were applied for 5 and 30 minutes respectively) compared  
293 to conventional extraction at 35°C for 2.5 h (43.9% of yield). In this case, the purity of lignin fraction was  
294 higher after US treatment and no significant changes from native lignin were observed.

295 More recently, Garcia et. al [54] evaluated the effect of US (420 W, 50/60 Hz) in the fractionation process of  
296 olive tree pruning residues. Different times (30, 60 and 120 minutes) and different solvent (water, NaOH 7.5%  
297 w/w and acetic acid at 60% v/v) were applied, using a US bath (420 W, 50/60 Hz) and a solid to liquid ratio  
298 of 1:10 (w/w). It was demonstrated that under US, lignin yield and selectivity in liquid fractions increased,  
299 compared to the reference sample conventionally treated. Additionally, a lower degree of cellulose degradation

300 and higher content of hemicellulose was found in US-treated samples. Moreover, the US-assisted process did  
301 not significantly affect lignin structure and thermal behavior, suggesting the suitability of the US technology  
302 for industrial applications. [54]

303 The effect of different frequencies (40 kHz, 376 kHz and 995 kHz) in US-assisted pretreatment of wheat straw  
304 was investigated by Bussemaker et al. [57] At each frequency, three different solid to liquid ratios (1/50, 1/20  
305 and 1/15 g/ml) were tested and, in addition, different particle sizes (0–0.5, 0.5–1, and 1–2 mm) were evaluated  
306 at 1/20 g/ml. In order to preserve the energy efficiency of the process, time extraction of 25 minutes was  
307 chosen. In fact, protracted times have been demonstrated to increase lignin re-condensation. Authors showed  
308 that delignification was enhanced at low frequency of 40 kHz up to 7.2% compared to the reference sample,  
309 as a result of mechano-acoustic effects, whereas high frequencies (995 kHz) favored carbohydrate  
310 solubilization.

311 Recently, a comparison among three different US reactor configurations (longitudinal horn, vertical immersion  
312 horn and ultrasonic bath) on the efficacy of sawdust delignification was described. [58] The effect of different  
313 operating parameters such as Na<sub>2</sub>CO<sub>3</sub> concentration (0.1, 0.15, 0.2, 0.25 M), H<sub>2</sub>O<sub>2</sub> concentration (0.2, 0.4,  
314 0.6, 0.8, 1 M) and biomass loading (2, 4, 6, 8, 10 wt%) has also been investigated. The optimized reaction  
315 conditions were found at 150 W for 70 minutes, with 0.2 M concentration of Na<sub>2</sub>CO<sub>3</sub>, H<sub>2</sub>O<sub>2</sub> 1 M and biomass  
316 loading of 10 wt%. Higher lignin yield was obtained with the longitudinal horn (87.4%), followed by ultrasonic  
317 horn (lignin yield of 85.1%) and ultrasonic bath (lignin yield of 82%), while only 42.4% of lignin yield was  
318 obtained with conventional method, confirming the process intensification benefits of US treatment.  
319 Additionally, the energy requirement for the delignification of sawdust was evaluated, finding that ultrasonic  
320 horn configuration presented lower power consumption ( $6.72 \times 10^6$  kJ/m<sup>3</sup>), followed by both longitudinal  
321 horn and ultrasonic bath ( $12.6 \times 10^6$  kJ/m<sup>3</sup>). However, authors declared that the higher energy consumption  
322 of longitudinal horn, compared to the immersion one, was due to the necessity of two additional stirrers on the  
323 extreme ends of the reactor to obtain a homogeneous mixing. Therefore, the efficacy of longitudinal horn is  
324 greater, since this configuration is able to process larger volumes with higher yields.

325 A US-assisted pretreatment of Vietnam's rice straw in NaOH 2M at 90°C was performed using an immersion  
326 horn (20 kHz 500 W) for a sonication time of 10, 20, 30, and 40 minutes.[59] The extraction was then carried



327 on in silent conditions at the same temperature for a total period of 1.5 h. Lignin yield with US irradiation was  
 328 enhanced; in particular, when US radiation was performed for 30 minutes, 84.7% of lignin was extracted. A  
 329 much longer time (2.5 h) was necessary to obtain the same yield with conventional treatment. Lignin obtained  
 330 by US-assisted treatment showed high purity and no substantial differences in the structure from the native  
 331 one, although it was found that US increased thermal stability and molecular weight of the recovered lignin.

332 Earlier research showed that ionic liquids (ILs) could catalyze the destruction of the intricate linkages of  
 333 lignocellulose to remove lignin. [60] In this context, Zhang et al [61] studied a series of acidic imidazolium  
 334 based ILs with various anions for corn stover fractionation under US irradiation (400 W) at 70°C for 3h. A  
 335 yield of 60.48% of isolated lignin was achieved when [HMIM]Cl was used as IL.

336 In general, it could be noted that US-assisted lignocellulose delignification is more efficient than conventional  
 337 treatments, exhibiting in many cases higher yields and selectivity of products in shorter times, meanwhile  
 338 saving energy (Table 2).

<i>Type of Biomass (% w/w)</i>	<i>US-assisted pretreatment</i>	<i>Chemicals</i>	<i>Advantages</i>	<i>References</i>
<b>Wheat straw</b> 38.9% cellulose 38.2% hemicellulose 17.2% lignin 2.1% ash 2.3% wax	20 kHz, 100 W Immersion horn	Methanol, 0.5M NaOH	US applied for 5 to 35 minutes lead to higher lignin yield (78.5% of the theoretical)	[55]
<b>Wheat straw</b> 38.8% cellulose 39.5% hemicelluloses 17.1% lignin 1.8% ash 2.2% wax	20 kHz, 100 W Immersion horn	KOH	Higher lignin yield (49.1% compared to 43% without US)	[56]
<b>Olive tree pruning</b> 32.31% cellulose 28.52% hemicellulose 27.60% lignin 2.80% ash 3.86% extracts 4.91% others	50/60 Hz, 420 W	Acetic acid, NaOH	Higher lignin yield and selectivity. Lower degree of cellulose degradation and higher content of hemicellulose	[54]
<b>Sawdust</b>	50 W longitudinal horn ultrasonic horn ultrasonic bath	Na <sub>2</sub> CO <sub>3</sub>	Higher lignin yield was obtained with US reactors (87.4%, 85.1% and 82% respectively), compared to conventional method (42.4%)	[58]
<b>Vietnam's rice straw</b>	20 kHz, 500 W	NaOH	US applied for 10 to 40 min led to higher lignin yield (84.7%)	[57]
<b>Corn stover</b>	400W	Imidazolium-based ILs	[HMIM]Cl combined with US catalyzed lignocellulose fractionation under mild reaction conditions (70°C). 60.48% of isolated lignin was obtained after 3 h of reaction.	[61]

340 Biomass pretreatments assisted by HC are more advantageous compared to the traditional methods since  
341 shorter time, lower energy consumption, and less chemical catalysts are usually required. Moreover, cavitation  
342 systems are highly attractive for scaling up and continuous processes thanks to their simple configuration.  
343 Recently, HC was used for the pretreatment of different lignocellulosic biomass with promising results; in  
344 particular, HC can lead to a higher lignin removal and an increased porosity of the remaining solid, enhancing  
345 the enzymatic hydrolysis for sugars production.[62,63] The efficiency of the HC process is strongly related to  
346 several key parameters, such as the viscosity of the fluid, the process temperature, particle size, and  
347 configuration of the system. In a recent study, sugarcane bagasse was treated by HC at 70 °C for 20 min in a  
348 low NaOH concentration (0.3 M) to improve the efficiency of alkaline pretreatment. [63] To perform the  
349 experiment, an orifice plate with 27 holes of 1 mm diameter was used. A lignin yield of 60.4% was obtained  
350 after 45 min of cavitation (0.48M of NaOH, 4.27% of S/L ratio), while conventional alkaline pretreatment led  
351 to 50.3% of lignin removal and US assisted to 59.6%. Moreover almost 93% yield of enzymatic digestibility  
352 was obtained under cavitation condition.

353 In another work, Kim et al. performed a HC-assisted alkaline (3% NaOH) pretreatment of reeds reaching  
354 53.4% of lignin removal and high glucose release (326.5 g/kg of biomass) after enzymatic hydrolysis.[64] A  
355 combined process of HC and enzymatic hydrolysis was recently performed as intensification of corncob  
356 pretreatment. The optimized reaction conditions (5% of biomass loading, 6.5 U g<sup>-1</sup> of enzyme loading) using  
357 an orifice plate led to 47,4% of delignification in 60 min, increasing the cellulose recovery from corncob  
358 (25.3%). [65] Recently, wheat straw was treated in alkali (KOH) and then subjected to HC using a rotor-stator  
359 cavitator to intensify the delignification step of paper manufacturing. [66] Researchers observed that the HC  
360 treating for 10–15 min improved the tensile index of the paper sheets up to 50% compared to conventional  
361 pretreatment.

362 Continuous processes are time and energy saving and the operational costs needed are lower compared to batch  
363 processes. However, currently, only a few continuous pretreatment methods with potential large-scale  
364 applications were reported. In this context, Terán Hilaes et al. described a continuous method for the  
365 fractionation of sugarcane bagasse (SCB). [67]A suspension of 1% of SCB in alkaline solution (0.3 mol/L of

366 NaOH, 0.78% of H<sub>2</sub>O<sub>2</sub>) was fed into the cavitation reactor at 200 mL/min flow rate (7.5 min as residence  
367 time). The released glucose and xylose in the subsequent enzymatic hydrolysis process were, in average, higher  
368 (41.7 g/100 and 19.1 g/100 g, respectively), than the ones from SCB pretreated in batch for 90 min  
369 (26.88 g/100 g and = 11.97 g/100 g, respectively) and the ones from non-treated SCB (9.32 g/100 g  
370 and 2.71 g/100 g respectively).

371 HC-assisted processes have therefore proven an attractive method for the intensification of pretreatment  
372 processes and an advantageous alternative when compared to conventional pretreatment processes as alkaline,  
373 steam explosion and organosolv, due to the shorter reaction time, higher efficiency and less amounts of  
374 chemicals. In addition, the lower energy requirement makes the scalability of this process easier and  
375 economically feasible in a lignocellulosic biorefinery.

### 376 3. Lignin Fractionation

377 Due to its highly complex structure and molecular weight dispersity, an efficient valorization of technical  
378 lignin has been found challenging. [68] Thus, preparation of lignin with a more uniform structure is desirable  
379 to obtain value-added products. To this end, membrane fractionation has been proposed as one of the best ways  
380 to achieve specific molecular weights and distribution.

#### 381 3.1 Membrane Lignin fractionation

382 Membrane filtration is a promising technology for the recovery and fractionation of lignin, since it presents a  
383 unique combination of economy, scalability, and flexibility in various industrial processes. [69]

384 Over the last decades, several membrane-based processes for the recovery and concentration of lignin solutions  
385 have been carried out, aiming to investigate the ability of membranes to isolate lignin. Due to the widely  
386 established process of Kraft pulping, most of the developed methods use black liquor as the raw material for  
387 lignin recovery while only a small part use spent sulfite liquor. Membrane processes were initially introduced  
388 to treat wastewater and therefore reduce water consumption by recycling clean water. However, last few  
389 decades tendency examined the implementation of membrane filtration in lignin separation and fractionation  
390 processes to enable its further valorization into phenolic compounds.[70] Membrane fractionation basically

391 consists in a separation process that employs a semipermeable membrane, which acts as a selective barrier for  
392 molecules. In comparison with other traditional processes of separation (evaporation or precipitation), it offers  
393 several advantages, such as continuous operation, the avoid of additional agents, lower energy consumption  
394 and the possibility of being combined with other techniques. However, some drawbacks could emerge,  
395 concerning the permeate flux decline, the lifetime of the membranes, and the low selectivity.[71,72]

396 Flux decline is one of the greatest challenges during filtration and is difficult to prevent because of the wide  
397 molecular weight distribution of the lignin molecules[69,73] The separation by molecular size depends on the  
398 material of the membrane (polymeric or ceramic). In particular, ceramic membranes are ideal for lignin  
399 recovery and fractionation because of their capability to tolerate extreme pH range and temperature along with  
400 their mechanical stability, though their selectivity is lower. [70] Different membrane geometries (flat disc,  
401 tubular) and different molecular weight cut-offs (MWCO) have been investigated. Moreover, membrane  
402 cleaning strategies have been developed to prevent fouling and re-establish membrane flux after lignin  
403 fractionation. A combination of rinsing and regular backflushing was shown to prevent fouling while  
404 increasing the average flux.[74] However, it is necessary to consider some aspects before performing a  
405 membrane separation process, such as lignin source, the pulping method used to obtain it, and the purpose of  
406 the process (e.g., lignin fractionation, carbohydrates separation, lignin concentration, etc.).[75] Moreover, the  
407 separation by molecular size also depends on membrane material. Lignin molecular weight is typically within  
408 the range of ultrafiltration (UF) technology (1-100 kDa); therefore, the dimensions are different from the other  
409 components of liquor enough to perform lignin separation and fractionation by UF membranes, leading to a  
410 more uniform lignin structure.[70]

411 Recently, Eucalyptus Kraft lignin fractionation using ceramic membranes with different MWCO (5, 15, and  
412 50 kDa) was reported. [76] Results showed that ultrafiltration is an efficient process for the treatment of this  
413 type of lignin. The obtained fractions were studied, showing that the lignin isolated with a 50 kDa membrane  
414 presented the highest molecular weight with higher content of carbohydrates and inorganics. In contrast, from  
415 the 5 kDa membrane low Mw lignin with low dispersity value was obtained; this type of lignin represents an  
416 important source of phenolic monomers after oxidative depolymerization.

417 A Bamboo Kraft lignin fractionation was performed by firstly dissolving the material in acetic acid to obtain  
418 a low viscosity solution and then fractionating it by UF into specific molecular weight fractions by sequential  
419 UF using membranes with different MWCO. [77] The three fractions presented different molecular weights  
420 with lower polydispersity compared to the non-treated Kraft lignin. The fraction obtained with a 5 kDa cut-off  
421 membrane showed the lowest molecular weight and higher amount of phenolic hydroxyl groups. Authors  
422 found that the addition of this low molecular weight lignin fraction into polyethylene provided a positive effect  
423 on the mechanical properties of the polymer.

424 D'Arrigo et al. [78] reported a multistep fractionation process of wheat straw grass lignin, using a mixture of  
425 water/ethanol as the solvent, followed by a microfiltration step through a 0.7  $\mu\text{m}$  membrane, aiming to remove  
426 insoluble particles. Afterward, two UF operations were performed with a polyether sulfone (PES) membrane  
427 with a MWCO of 3 and 1 kDa. The molecular weight of recovered fractions after permeation decreased  
428 progressively. In particular, the filtration through a 3 kDa cut-off membrane leads to the recovery of a high  
429 molecular weight fraction that could be employed as macromonomer of lignin-based polymer. Furthermore, it  
430 allowed the retrieval of a low molecular weight fraction consisted in high value-added chemicals. The same  
431 research group performed a two-step organic solvent extraction of wheat straw lignin, followed by two UF  
432 steps using cellulose-based membranes (MWCO of 2 and 5 kDa).[79] Lignin stream was obtained by Soxhlet  
433 extraction using 2-butanone as the solvent. This step allows the transfer of lignin soluble components to the  
434 liquid phase, while separates solid residues. Afterwards, two sequential UFs generated two different lignin  
435 fractions with narrow molecular mass distribution.

436 A recent study compared acid precipitation and solvent fractionation with UF fractionation of Kraft softwood,  
437 organosolv hardwood, and grass lignin into low, medium and high molecular weight fractions. [80] Mass yield,  
438 structural (molecular weight distribution, elemental composition) and functional (OH-group number) of the  
439 obtained fractions were examined. Ceramic tubular membranes with MWCO of 1, 15, 50 and 150 kDa were  
440 used in the UF step. In general, authors reported that solvent extraction and acid precipitation provided better  
441 separation with better mass distribution, polydispersity, and functional OH-groups distribution.

442 Among lignin biorefining processes performed under H<sub>2</sub>-pressure (e.g., reductive catalytic fractionation,  
443 RCF), catalytic upstream biorefining (CUB) process employs H-donor as solvent in conjunction with Ni Raney

444 catalyst aiming to depolymerize lignin. Recently, a two-step membrane fractionation of lignin liquor from  
445 CUB process was exploited. [81] Isopropanol (2-PrOH) was employed both as a component of the lignin  
446 extracting liquor (2-PrOH/H<sub>2</sub>O 7:3, v/v) and as the H-donor for the selective hydrodeoxygenation process.  
447 The membrane cascade assisted both the concentration of the monophenol-rich fraction and the separation  
448 from the liquor. Membrane fractionation offers a suitable technology for lignin components separation from  
449 the liquor. Moreover, further chemicals addition in these processes is avoided, making their further utilization  
450 highly attractive.

#### 451 4. Depolymerization of Isolated Lignin

452 The pretreatment processes aiming to extract lignin often produce lignin polymers which has undergone  
453 multiple chemical modifications, resulting in a heterogeneous mixture difficult to analyze. Thus, the key to  
454 lignin valorization passes through the selective depolymerization and the recovery of the end-products as  
455 individual lignols. In fact, the depolymerization of lignocellulose generates a variety of compounds that can  
456 be used as building blocks for valuable chemicals, fuels, polymers, or pharmaceuticals. [3,19] Lignin phenolic  
457 units have found, until now, only limited market application: they can be converted into BTX (benzene, toluene  
458 and xylene) or oxygenated compounds (e.g., phenols, aromatic alcohols, aldehydes, quinones, etc.) however,  
459 they are still overpriced compared to the petrol-derived analogues and the direct production of aromatics from  
460 lignin is typically low.[82] As above mentioned, one reason regards repolymerization of the reactive  
461 intermediates that is the cause of low aromatic yields.

462 The development of effective catalyst and new technologies are the keys to the successful conversion of lignin  
463 into high-quality products: moreover, bio-oil yield depends on various factors such as particle size,  
464 temperature, and reaction catalyst. Among them, heating rate is one of the most critical factors that can affect  
465 the composition of bio-oil. [83,84]In fact, higher heating rate (> 100 °C/s) favors the production of bio-oil  
466 compounds whereas a low heating rate leads to char formation: with higher heating rate, the rupture of various  
467 chemical bonds can occur simultaneously, reducing the production of stable oligomers, which can pave the  
468 way to undesirable solid products.

469 In addition, several processes such as pyrolysis or acid/base hydrolysis are used for the depolymerization of  
470 lignin: although the obtained products are prone to chemical instability due to their high oxygen content.

471 Therefore, oxygen content in aromatic products must be reduced before utilization: in this context reductive  
472 conversion of lignin, could be an effective strategy for lignin valorization, since it combines lignin  
473 depolymerization and deoxygenation in one process, resulting in more stable aromatics with higher heating  
474 value.

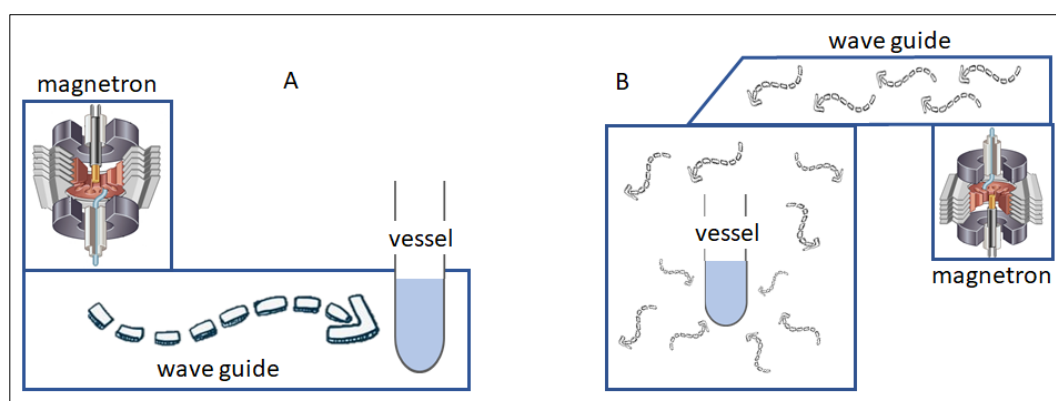
475 Thus, the development of new processes coupled with effective catalytic systems could not only reduce the  
476 difficulty in the lignin depolymerization, but also increase product yields improving the economy of the  
477 process. Existing technologies for biomass deconstruction and lignin depolymerization have, in fact,  
478 limitations related to efficiency and energy consumption. Therefore, process intensification through  
479 microwave (MW) technology could represent an advantageous strategy for time and, consequently, energy  
480 saving, including fast heating that can reduce undesired side-reactions.

#### 481 4.1 MW technology

482 The use of MW has gained increasing interest in the field of biomass valorization in recent years. The  
483 interaction of microwaves with the matter results in dielectric heating, as an alternative to the traditional  
484 convective heating methods. In fact, the latter are based on superficial heat transfer, which is a rather slow and  
485 inefficient way for transferring energy into a reaction mixture. Nevertheless, microwaves exploit the direct  
486 interaction between the object and the applied electromagnetic radiation. This generates a homogeneous  
487 volumetric (non-superficial) heating.

488 The first use of MW in organic synthesis leads back to Gedye e Giguère, who noted that MW heating  
489 significantly enhanced the reaction rate. [85][86] MW heating also exhibits a positive influence on chemical  
490 reactions, enhancing yields and selectivity.[87] [88] Microwaves are electromagnetic radiations with  
491 frequencies between 0.3 and 300 GHz. The frequency used in MW reactors is fixed at 2.45 GHz; consequently,  
492 the associated energy is too low to break a chemical bond. Therefore, the effects of MW are due to the efficient  
493 heating of molecules by two mechanisms: dipole rotation and ionic conduction. [89] The first one describes  
494 the tendency of dipoles to constantly align themselves with the MW electric field by rotation, causing friction  
495 that generates heat. In ionic conduction mechanism, ionic particles oscillate under the influence of MW electric  
496 field, leading to the formation of a current. This current is subjected to internal resistance due to collisions  
497 between particles, which generate heat.

498 There are several types of MW reactors which differ in terms of MW source, cavity design, scale and  
499 automation. However, mono-mode and multi-mode are the two categories in which they are classified. Mono-  
500 modal reactors are designed in order to create a standing wave, which is directly focused on a single vessel  
501 (Figure 9A). Among many advantages, the most important is the high heating rate even though only one vessel  
502 can be irradiated, which makes mono-modal reactors ideal for reaction optimization and small-scale  
503 applications. In multi-mode reactors, the sample is placed inside a cavity where the waves are reflected,  
504 generating a disordered dispersion of radiation, which increases the area of effective heating (Figure 9B). Thus,  
505 a multi-mode MW reactor can accommodate a higher number of samples simultaneously, making these tools  
506 perfect for the screening of reaction conditions. Moreover, multi-mode MW are usually designed for scaling  
507 up reactions, unlike single-mode apparatus. However, heating control of samples is a major limitation of multi-  
508 mode apparatus because of temperature uniformity due to the chaos of the waves.



509

510

Figure 9: Monomodal (A) and multimodal (B) microwave reactors

511 Azuma et al.[90] introduced MW for biomass pretreatment before enzymatic hydrolysis for the first time in  
512 late 1980s. It was found that MW treatment in the presence of water initiates hemicellulose and lignin  
513 degradation, leading to a higher saccharification rate, compared to conventional processes such as steam  
514 explosion. A few studies reported the use of MW heating for lignin depolymerization[91,92], documenting a  
515 significant decrease in time required for biomass deconstruction. Furthermore, MW promote selective bond  
516 cleavage during lignin depolymerization, leading to a narrow molecular weight distribution compared to  
517 conventional heating techniques. Probably, this is due to the stretching of certain lignin bonds under the electric  
518 field imparted during MW irradiation, that could increase the probability of their breaking.



## 519 4.2 MW specific effects

520 The main advantage of using MW as heating technology relies in the reduction of time reaction. However, the  
521 rate-acceleration typically observed in microwave-assisted reactions may in some instances also lead to higher  
522 selectivity compared to the conventional heating processes. This is the reason why dielectric heating is claimed  
523 to have two different effects: thermal and non-thermal.[88] Thermal effects are those derived from microwave  
524 dielectric heating, which may cause different temperature regimes. Non-thermal effects, also called “specific  
525 microwave effects”, are claimed when a reaction performed under microwave conditions behaves differently  
526 from the same reaction performed at the same temperature under conventional heating. For example, changes  
527 in reactivity and selectivity could be explained by the direct interaction between microwave radiation and the  
528 reaction system.[93,94] However, the existence of non-thermal effects is still a controversial question.[87,93]  
529 One of the reasons lies in the fact that the energy emitted from a microwave photon is too low to have any  
530 effect in breaking a chemical bond (0.0016 eV). Moreover, the commercially available microwave reactors are  
531 not suited to perform reliably study of bulk thermal phenomena associated with rapid heating. Other  
532 explanations refer to the experimental errors in temperature measurement. However, many researchers claimed  
533 that a direct interaction of the electromagnetic field with specific molecules could explain unexpected results  
534 which cannot be a consequence of thermal gradients.[95] Anyway, the rate acceleration can be attributed to  
535 thermal effects. In fact, microwave heating profiles are not easily reproducible by conventional techniques.  
536 Moreover, it has been demonstrated that heating profile can affect the product formation. [96] In addition, in  
537 multi-modal microwave reactors the presence of hot spots could occur, giving rise to local temperatures which  
538 are higher than the one measured in the bulk. These local hot spots, which are not accurately measurable, could  
539 explain unexpected results in microwave reactions. As a matter of fact, the existence of microwave specific  
540 effects appears to be a continuing debating area.

## 541 4.3 MW-assisted lignin depolymerization

542 Over the past few decades, the depolymerization of isolated lignin to aromatics became an attractive approach  
543 for lignin valorization into value-added chemicals. However, depolymerization strategies lack in selectivity  
544 towards aromatics compounds. Moreover, the cleavage of lignin linkages is still a difficult issue, since most  
545 of C-C bonds persist after depolymerization processes.[21] Lignin depolymerization approaches include acid

546 and base hydrolysis, oxidation and hydrogenation. Among these, lignin hydrogenation could selectively cleave  
547 ether linkages into phenols partially avoiding repolymerization and self-condensation, leading to higher  
548 monomer yield. [97] In recent years, several strategies have been developed that employ molecular hydrogen  
549 in heterogeneous catalyzed processes. In particular, hydrogenolysis and hydrocracking provide lignin linkages  
550 cleavage by the addition of hydrogen to the reaction mixture.[98] Microwave-assisted technology has been  
551 recently proved a successful tool biomass conversion thanks to its fast and highly efficient heating compared  
552 to conventional systems.[99]

553 Microwave-assisted lignin depolymerization in several organic solvents, acids and bases has been known to  
554 efficiently afford aromatic monomers and oligomers at relatively mild conditions (<200 °C).[100,101]  
555 Furthermore, microwaves accelerate lignin model compounds conversion into phenols, simultaneously  
556 increasing product selectivity. [99] An important aspect to consider for heterogeneously catalyzed lignin  
557 hydrogenation consist in the mass transfer to the catalyst surface of insolubilized lignin and molecular  
558 hydrogen. Hydrogen pressure is also a key parameter, as it can lead to undesired products, when it is too high.  
559 Nevertheless, for a sustainable approach it is necessary to reduce the consumption of fossil-derived hydrogen  
560 which negatively affects the carbon footprint of chemical processes.[102]

561 For these reasons, recent strategies consist in the use of hydrogen-donor systems (e.g., alcohols, formic acid)  
562 as the solvent. Formic acid (FA), which is a bulk industrial chemical, is cheaper than any H-donor solvent and  
563 safer than molecular hydrogen. At elevated temperature it decomposes into CO<sub>2</sub> and H<sub>2</sub>, even though in some  
564 cases it could also go to CO[103]. Besides, it can be derived from renewable resources. Hydrogen donor  
565 solvents are not only suitable to transfer hydrogen in the lignin depolymerization process, but they also enhance  
566 lignin solubility. For instance, the use of alcohols as H-donor solvents have gained increasing attention in  
567 lignin hydrogenation due to the higher lignin solubility, which enhances the contact with the catalyst, and the  
568 capability of suppressing repolymerization reactions, which can lead to the undesired bio-char.[104] Therefore,  
569 hydrogen donor solvents, coupled with heterogeneous catalysts, could promote the selective cleavage of C-C  
570 and ether bonds in lignin.

571 In recent literature, hydrogen donor solvents combined with microwaves have been reported as an efficient  
572 tool for the lignin liquefaction under mild reaction conditions, with or without the presence of catalysts [105–

573 108] Toledano et al. [106] studied the effects of the type of metal catalyst in a microwave-assisted hydrogen-  
574 free depolymerization of organosolv lignin. Catalyst screening included different metal nanoparticles: Ni (2,  
575 5, and 10 wt.%), Pd (2 wt.%), Pt (2 wt.%), and Ru (2 wt.%) supported on Al-SBA-15. Depolymerization  
576 reactions were conducted in a multimode microwave reaction system with a 400W constant power.  
577 Experiments were performed for 30 min at average temperature of 140°C, using formic acid as H-donor. The  
578 highest bio-oil yield of 30 wt.% was obtained when Ni10%AlSBA was used as the catalyst, while 5 wt.% of  
579 bio-oil yield was obtained when Pd2%Al-SBA was used.

580 When formic acid was used, bio-char formation was lower as compared to other H-donors. This could be  
581 ascribed to the decomposition of formic acid into gases (e.g., CO, CO<sub>2</sub> and H<sub>2</sub>) during the lignin  
582 depolymerization, whereas different H-donor solvents could react with lignin radical fragments leading to the  
583 formation of bio-char. Shen et al.[107] performed lignin depolymerization in formic acid at 130°C and 30 min,  
584 using HUSY zeolite as the catalysts. The yield in bio-oil was enhanced in the presence of the catalysts.  
585 Moreover, bio-oil yield increased to 88.28 wt% (15.36% of aromatic monomers and 67.52% of oligomer  
586 fractions), when HUSY modified by 0.2 mol/L oxalic acid was used.

587 Reaction time and temperature effects on the phenolic yield compounds from the microwave-assisted acidic  
588 solvolysis of black-liquor lignin were also investigated. [107] Depolymerization occurred in a microwave  
589 digester at a reaction temperature of 110–180°C and a reaction time of 5–90 min. Results indicated that the  
590 yield of liquid products increased when the reaction temperature was below 160°C and decreased when the  
591 reaction time was superior to 30 min. Depolymerization and repolymerization reactions were both enhanced  
592 by increasing the temperature and prolonging the reaction time. Hence, the key to obtain high yield of mono-  
593 phenolic compounds is to avoid re-condensation reactions.

594 Vinu et al.[109] investigated the microwave-assisted degradation of lignin in the presence of different organic  
595 solvents including ethylene glycol (EG), dimethyl sulfoxide (DMSO) and dimethyl formamide (DMF) under  
596 moderate conditions (100–140 °C, 20–80 min). Molecular weight (Mw) reduction of lignin was observed in  
597 all the solvents, and it was found to be highly dependent on the solvent polarity and temperature. Results  
598 showed a molecular weight (Mw) reduction at 120°C in polar protic solvents, whereas the reduction of Mw in  
599 aprotic polar solvents increased at higher temperatures, showing that the combination of microwave and polar

600 solvent greatly affected the decrease of Mw. Moreover, in EG, the cleavage of C-O bonds, leading to the  
601 formation of guaiacol, was preferred over C-C bond, while in DMSO anisole, guaiacol, syringaldehyde and  
602 acetosyringone were obtained by cleavage of both C-O and C-C bonds.

603 Microwave-assisted lignin hydrogenation using isopropanol was investigated, finding the highest yield of bio-  
604 oil (45.35 wt.%) at 120°C with the reaction time of 30 min, together with 38.65% of char as and 14.73%  
605 residual lignin.[110] Prolonged times increased the formation of biochar, whereas the bio-oil yield decreased,  
606 confirming that protracted reaction time leads to condensation of monomers to oligomers.

607 Shao et al. [111] proposed the depolymerization of alkaline lignin in methanol/formic acid media. Formic acid  
608 acted mainly through acid-catalyzed cleavage of the linkages in lignin. Oligomers in bio-oil were mainly  
609 composed of dimers and trimers, according to the MALDI-TOF MS analysis. Different FA/lignin mass ratio,  
610 reaction temperature and reaction time were applied, aiming to investigate their effects on product yield and  
611 distribution. The highest bio-oil yield of 72.0 wt.%, including 6.7 wt.% monomers, was achieved at 160 °C  
612 and a FA/lignin mass ratio of 4 after a reaction time of 30 min. Additionally, the bio-oil yield was compared  
613 with the one obtained at the same conditions under conventional heating: 41.1 wt.% yield of bio-oil including  
614 0.89 wt.% of monomers was obtained, indicating that microwave significantly improved bio-oil yield.

615 Recently, a comparative study on various alcohols in microwave-assisted lignin depolymerization has been  
616 carried out. [112]Methanol and ethanol showed higher conversion rate of 84.86% and 84.22%, respectively  
617 and lower Mw of liquefied products, when compared with butanol, ethanediol and isopropanol. The reason  
618 lies in the fact that the Mw of methanol and ethanol is lower, providing higher permeability and fluidity. In  
619 addition, in lignin depolymerization processes, usually alcohols are incorporated into the lignin-derived  
620 products within acidic medium; consequently, repolymerization of lignin-degraded products is avoided and  
621 the conversion of lignin into low molecular weight liquid products is enhanced.[113] Lignin conversion when  
622 butanol was used counted only 49.34%; this could be explained by the increased lengthiness of the carbon  
623 chain, which provides more hydrophobic alcohols. Higher hydrophobicity is not beneficial for the conversion  
624 of biomass, especially when combined with microwave dielectric heating.

625 In summary, low molecular alcohols and acids demonstrate to be promising in the microwave-assisted lignin  
626 depolymerization processes, both as solvents able to promote solvolysis and as H-donors for reductive  
627 depolymerization. Thus, their versatility should be further investigated for effective liquefaction of lignin.

## 628 5. Scale-up

629 In the biorefinery concept the exploitation of biomass-derived feedstocks, such as lignocellulosic materials, is  
630 the key for the sustainable production of a plethora of useful compounds which are, until now, derived from  
631 petroleum. However, the estimated selling price of the products obtained from renewable sources would not  
632 compete with the prices of the ones produced by fossil fuel, since the cost of the feedstock is typically higher.  
633 Hence, lowering the price of bio-derived product is the bullet point of biorefinery. [114,115]

634 In this framework, green technologies such as MW, US and HC have recently showed promising results in the  
635 valorization of lignocellulose. However, these methods need to be deeply studied for their techno-economic  
636 feasibility at industrial scale. Notable advantages of the above-mentioned techniques lie in the higher  
637 selectivity, shorter reaction time and often higher yields, which make these processes highly attractive for  
638 industrial scale applications. However, it is also fundamental to consider the economies and profitability of the  
639 scaling-up.[28] Usually, the applicability of a new technology at industrial scale requires techno-economical  
640 assessments and energy consumption studies (Figure 9).

641 A necessary preliminary step to efficiently process and transform biomass at industrial scale, involves size  
642 reduction, through which biomass can be, first of all, stored and easily managed. Without providing a suitable  
643 grinding degree, biomass cannot be efficiently converted: in fact, particle size can affect biomass conversion,  
644 since the yield of volatiles decreased with the increasing of biomass dimension. [83]However, grinding is a  
645 highly energy consuming process; therefore, it is imperative to find the most suitable parameter conditions in  
646 order to increase the efficiency of the process.[115]

647 US and HC are consolidated technologies for PI, since the high-energy hot spots generated by cavitation  
648 strongly promote a faster and more efficient disruption of the lignocellulose matrix, increasing the accessibility  
649 for further processing steps with generally shorter reaction times, milder conditions and lower energy  
650 consumption. Generally, US systems are less energy efficient than HC reactors: the principal limitation

651 consists in the low pressure-wave penetration through reaction mixture. Consequently, cavitation only occurs  
652 near the transducer. HC reactors have been reported to be a realistic tool for large scale applications and an  
653 alternative to acoustic cavitation for the intensification of lignocellulosic processes, since the scaling up is  
654 comparatively easier and the only energy consuming device is the one related to the rotor-stator  
655 reactor[63,116]. In fact, these systems are simply equipped with a pump, a tank, pipes, valves and a cavitation  
656 device (orifice plate or venture tube), while the limitations of using US on large scale consist in a lower power  
657 efficiency, higher fabrication costs and lower irradiating surfaces.[116]

658 Moreover, in HC reactors speed rotation, percentage of biomass and the time of treatment can be easily  
659 optimized depending on the types of biomasses. In fact, the selection of an optimal design configuration of the  
660 reactor is necessary to improve cavitation and achieve cost-effective operation. Rotor-stator reactors are the  
661 most attractive ones to operate in continuous or semi-continuous processes, while orifice plate setup appears  
662 to be the most flexible device for higher scale operations, since the intensity of cavitation can be simply  
663 monitored, and the consuming energy can be reduced.[117]

664 The two major processes used in the pulp and paper industry to recover lignin from the spent liquor are the  
665 sulfite pulping process and the Kraft process[118]. Both these processes involve lignin solubilization, its  
666 separation from the insoluble cellulose and hemicellulose by filtration and the following recovery by  
667 precipitation. The major drawback for an improved valorization of lignin at industrial scale consists in the  
668 broad molecular weight distributions, which highly affects the reactivity of lignin, suggesting membrane  
669 fractionation as a necessary step aiming to obtain lignin with more uniform characteristics, which could lead  
670 to more reproducible processes. Furthermore, the separation of lignin from the black liquor in the pulp mill  
671 process is relatively easy: suitable membrane cut-offs allow an efficient control of the molecular mass  
672 distribution, with no need of pH modification or temperature variation, ensuring low energy requirements and  
673 higher product value. [119] Generally, membrane filtration is used in pulp mills to recover the spent pulping  
674 liquor in order to burn it and use it as external fuel. Thus, to overcome this strategy and valorize lignin at  
675 industrial scale, alternative methods are required. Spent liquor composition varies depending on the type of  
676 wood and process performed and usually consists of 60 % lignin, 30 % sugars and 10 % inorganic  
677 materials.[120]

678 Membrane filtration could be then used to separate the liquor into more purified lignin fractions, which are  
679 commercially more valuable and could be used in several applications: (as dispersing agent, precipitates,  
680 binders and adhesives). For example, vanillin synthesis from guaiacol accounts for 85% of the world stream,  
681 while only the 15% is produced from lignin recovered by membrane filtration from spent sulphite liquor at  
682 Borregaard Industries, in Norway.[118] Hence, low costs and high energy-efficiency of membrane separation  
683 process are fundamental requisites which can define whether concentration and fractionation could be  
684 economically feasible; for instance, a comparison between lignin precipitation and ultrafiltration showed that  
685 the first one is cheaper; however, the removal of high molecular-weight lignin by ultrafiltration was found to  
686 be feasible and economically attractive in a simulation study. [119]

687 An ongoing challenge is related to membrane fouling and the related flux decline caused by deposition of  
688 particles, macromolecules, salts, and others; therefore, it is highly difficult to prevent. Moreover, the necessity  
689 of frequently cleaning membrane plates is the principal cause of the increasing costs.

690 Recently, US-assisted filtration has shown to be an effective tool for fouling control by accelerating the  
691 permeate flux towards membranes, removing particles in the pores and on the surface thanks to the action of  
692 cavitation, increasing the overall filtration performance. [121–123] However, a critical issue concerns  
693 membrane damage due to the intense cavitation, thus US intensity should be chosen aiming to both minimize  
694 energy consumption and potential membrane damage. Moreover, the economic value and industrial  
695 application feasibility are challenges that must be still addressed: in fact, US energy requirements could be in  
696 contrast with the applicability at industrial scale. However, at present, there are no studies on the viability of  
697 US-assisted membrane cleaning and its effective application at large-scale membrane processes. In general,  
698 the fractionation capability with low chemicals loadings and low energy consumption, make membrane  
699 separation an excellent tool in the biorefinery process and an economically feasible process at industrial  
700 scale.[76]

701 Concerning MW technology, time saving, and product selectivity are the principal advantages, together with  
702 the relatively simple equipment and the easiness to control reaction parameters. Therefore, these aspects can  
703 significantly reduce the cost of final products making large-scale production feasible.[99,114] Furthermore,  
704 the fast-heating rate and the rapid cooling, by turning off MW, can reduce the formation of char in lignin

705 depolymerization. In addition, to achieve optimal lignin conversion, depolymerization strategies require low  
706 temperature aiming to avoid condensation of lignin intermediates. Thus, new generation of MW devices  
707 provide more reproducible experiments thanks to the possibility to better control reaction parameters.[124]  
708 Therefore, process intensification based on MW heating, together with the developing of pilot scale continuous  
709 apparatus, is gaining increasing interest.[125,126]

710 However, even if it is recognized that MW provide better quality of bio-products in shorter time, MW processes  
711 at industrial scale are not common. In fact, the implementation costs for MW apparatus are still elevated since  
712 this technology is in its early stages. Moreover, the energy efficiency of MW-assisted reactions should be  
713 considered case-by-case; it has been demonstrated that processes performed with laboratory scale MW reactors  
714 are typically energy inefficient. Nevertheless, when moving from lab scale to kilogram scale and from single  
715 mode to multimode reactors, MW heating processes become, in general, more energy efficient than the  
716 conventional ones.[127] Bermúdez et al. found that the energy consumed per gram of sample is dependent on  
717 the amount of sample used: consumption decreases when moving from few grams to 50-100 g. Moreover,  
718 when moving to kilograms scale, the energy consumption is almost constant, indicating that when a MW  
719 apparatus is not used at its maximum loading capacity, there will be a significant waste of energy. [127] In-  
720 depth studies on the techno-economic feasibility at industrial scale of enabling technologies have not been  
721 performed in detail yet. The reason lies in the fact that a limited number of scientific studies has been conducted  
722 at large scale up to date. Moreover, pilot scale processes are usually performed on modified laboratory  
723 apparatuses, thus, there is still a large gap between laboratory research and industrial applicability. However,  
724 enabling technologies have widely demonstrated to be highly attractive and potentially feasible for process  
725 intensification of biomass. Nevertheless, there is still the necessity for a multidisciplinary approach for the  
726 implementation of new technologies at industrial scale.



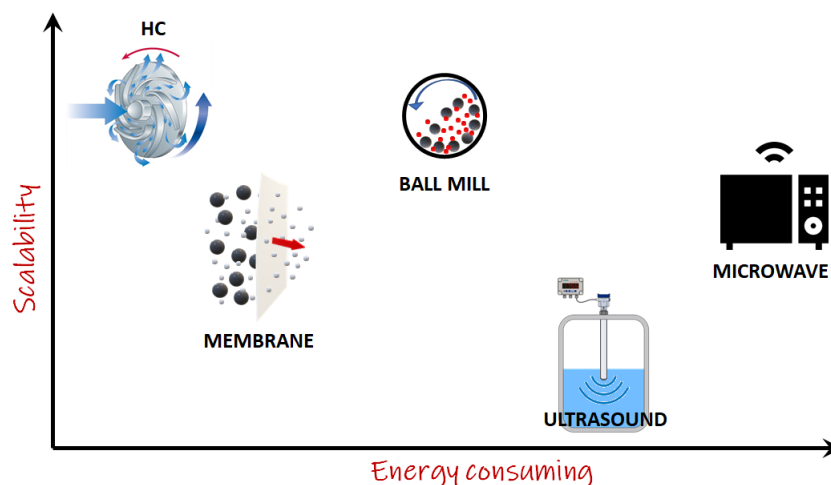


Figure 10: Comparison of enabling technologies in terms of scalability and energy consumption.

## 6. Future perspectives

The development of systems that can convert lignin into valuable products should be the goal of future research efforts for a sustainable lignin reductive process and its feasibility at industrial scale: efforts should include higher conversion with high product yield and selectivity, recyclability of solvent and catalysts and facile product isolation.

Therefore, the valorization of lignin into high-added value products requires the implementation of new enabling systems. A crucial step in the process concerns the study of dimeric model compounds: C-O-C linkages in fact constitute a significant fraction in lignin, thus, future studies should take into account the conversion of more suited model compounds and preferably real lignin substrates.[128] It is known that the major drawback in lignin depolymerization consist in C-C bonds formation during the reaction process, therefore, extensive research has been made on the cleavage of C-C linkage dimers to improve the effective depolymerization of condensed lignin such as Kraft lignin. [129]Hence, aside from studying the conversion of  $\beta$ -O-4 model compounds, future research should point fractionation strategies that prevent lignin re- condensation.

In this context, reductive catalytic fractionation (RFC) has gained increasing attention, since lignin isolation and depolymerization are simultaneous processes, resulting in less side reactions that can led to char formation as solid by-product.[130] Another strategy to avoid C-C bonds formation concerns the use of

746 stabilizing agent in the reaction media. It is known that, with respect to oxidative depolymerization,  
747 hydrogen plays an important role in stabilizing reactive intermediates, acting as radical scavenger. Recently,  
748 aldehydes were studied as protecting group to stabilize lignin's  $\alpha,\beta$ -diol group during extraction process, in  
749 order to prevent condensation reactions, resulting in higher aromatics yields. In fact, in aldehyde-stabilized  
750 lignins, the  $\beta$ -O-4 bonds are almost completely preserved as acetal structures, thus the subsequent  
751 hydrogenolysis gives lignin monomers at near-theoretical yields.[131]

752 Hence, future attention must be paid to lignin extraction process aiming to obtain isolated lignins with low  
753 degrees of structure modifications. In this framework, enabling technologies coupled with recent strategies in  
754 depolymerization processes could be a winning approach for biomass valorization.

## 755 CONCLUSION

756 In order to improve the sustainability and efficiency of wood-based biorefineries, lignin valorization strategies  
757 should be considered and implemented, since the capital investment strongly depends on integrated processes  
758 of biomass fractions upgrading (cellulose, hemicellulose and lignin).

759 Several problems are related to valorization of lignin concerning mainly its recovery from product stream with  
760 high purity, the preserving of native structure, since structure modification can alter its reactivity. Although  
761 there are various methods to overcome these problems, they are usually only partial solutions since  
762 heterogeneous structure and unique reactivity limit their use at industrial level. Existing methods can only  
763 partially solve these problems. Though, promising approaches are emerging which could allow lignin  
764 valorization into molecules for specific applications.

765 In lignin valorization protocols, the most important aspect to consider should be the treatment cost. In fact, up  
766 to now, the knowledge about lignin structure has paved the way for new sustainable green routes to produce  
767 bioenergy and value-added chemicals, aiming to overcome the disadvantage of conventional reactors.  
768 Furthermore, the limitations in achieving high product selectivity are the major bottleneck in lignin  
769 valorization.

770 Over the last decades, enabling technologies such as US, HC, MW and milling have demonstrated to lead to  
771 better results both in biomass pretreatment and in lignin depolymerization, thanks to the optimal mass and heat

772 transfer, which allow the enhancement of biomass exploitation, reducing time reaction and energy  
773 consumption. However, the efficiency of new technologies is prone to be opposed to energy cost requirements.  
774 Therefore, a comprehensive understanding on the techno-economic aspects of unconventional technologies is  
775 crucial to an optimal design of scaling up procedures, aiming to a full industrialization.

776 In conclusion, process intensification through the development of milder and greener processes for biomass  
777 fractionation and lignin depolymerization should be rapidly implemented in biorefineries context, to make  
778 them a promising alternative to traditional oil refineries.

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