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Production of levulinic acid and alkyl levulinates: A process insight

Daniele Di Menno Di Bucchianico[a,b], Yanjun Wang[c], Jean-Christophe Buvat[a], Yong Pan[c], Valeria Casson Moreno[b], Sébastien Leveneur*[a]

The use of lignocellulosic biomass in the chemical industry has increased due to its non-competition with the alimentary sector. Several platform molecules can be produced from this biomass. Among them, levulinic acid and its esters have been produced in industrial scale. There are some reviews on the production of levulinic acid (LA) but few on the production of levulinates (LEs). To fill this gap, this review was written by also considering the environmental aspects. In the first stage, the recent progress on the production of these platform chemicals was discussed. Production processes of alkyl levulinates from levulinic acid esterification, precursors (HMF, furfural, etc.), sugar monomers (glucose, fructose, etc.), cellulose, hemicellulose, or cellulose directly from lignocellulosic biomass were described. In the second stage, process separation and purification of LA and LEs were discussed. The final stage proposed an economic and environmental consideration for the production of these chemicals.

1. Introduction

At the present moment, the global primary energy consumption is estimated to be 160 × 10^{18} J per year and fossil sources still cover 80 % of this demand, playing the role of the largest contributor to greenhouse gas emissions in EU,[1] whereas renewable biomass contributes between 10-14 %.[2]

With a potential contribution estimated up to 30-40 % in the next 30 years, biomass is the main renewable source of energy (with an actual share of almost 60 % in EU) and platform chemicals in Europe.[3,4]

According to the Paris agreement and its objective to keep the global temperature increase below 2 °C by reducing the greenhouse gas emissions, the European Union approved a new sustainable development scenario by setting up to reach 55 % greenhouse gas reduction by 2030 compared to 1990, with a binding renewable energy target of 32 %, and to achieve the climate neutrality by 2050 (NZE2050).[5,6]

Although renewables overcome fossil fuels by one percentage point (38 % against 37 %) for the European production of electricity for the first time in 2020, the energy transition is still too slow and has to be accelerated to reach the ambitious targets, and the biomass plays a crucial role in this change.[7]

Since the beginning of the century, forestry, followed by specific crops and by-products, is the source that contributes most to the supply of biomass, specifically lignocellulosic biomass (LCB), overcoming the food versus fuel conflict.[4,8]

Regarding other renewable resources (e.g. solar, wind, wave, geothermal, etc.), lignocellulosic biomass (LCB) is the only carbon-fixing renewable resource generated from carbon dioxide and water through photosynthesis.[9–12] The primary products of photosynthesis are sugars (C6 and C5) that form the main components of the vegetal cell wall: cellulose (by polymerization of glucose, 25-55 %), hemicellulose (a polymer of glucose and xylose, 24-50 %), and lignin (a highly cross-linked polymer built of substituted phenols, 10-35 %).[2,10,13,14] Therefore, biomass is mainly made of carbohydrates, divided into storage polysaccharides (e.g. starch and inulin), disaccharide, sucrose, and structural polysaccharides such as cellulose and hemicellulose. The other contributions to biomass composition are triglycerides (from fats and oils), proteins, terpene hydrocarbons, waxes tannins, and inorganic matter.[2,14]

As a consequence of biomass composition, the transition from a fossil-based to biomass-based chemical industry would imply to switch from hydrocarbons to carbohydrates as key chemicals.[15] Carbohydrates (sugars) could be the starting point for the production of biofuels and biochemicals in the same way that fossil hydrocarbons are. According to the Green Chemistry Principles (Fig. 1 and Table 1), the use of renewable feedstocks should be preferred rather than depleting ones.[16] Defined by the International Energy Agency (IEA) as "the sustainable processing of biomass into a spectrum of marketable products (food, feed, materials, chemicals) and energy (fuels, power, heat)",[17] the biorefinery concept has foreseen the co-manufacture of biofuels and biochemicals or intermediates, also referred to platform chemicals, similarly to the petrochemical industry.[2] Indeed, biobased products have gained increasing importance in recent years to improve environmental issues by reducing the use of fossil sources.[3]

In this panorama, LCB is an abundant and relatively cheap carbon source that can produce biofuels, materials and biochemicals.[3] However, the considerable benefits of using economical renewable feedstock must face several challenges; one of those is the demand for reliable, sustainable and cost-effective biomass feedstock supply-chains that affect the cost-competitiveness of the biorefinery process, being an essential pre-requisite for its success.[18,19] A combination of "many-to-few" and "one-to-one" harvesting-handling-processing-storage-transport operations feature the logistic chain.[20] In this complex system, biomass transportation from the source to the final processing point is the major cost item, accounting for between 13 % and 28 % of biomass production and supply, depending on the biomass densification and transport mode.[18] Lignocellulosic substrates are characterized by low bulk density (64-224 kg m^{-3}), low energy density (10-17 MJ kg^{-1}), irregular form and high moisture content.[21] These factors complicate the transport step, requiring pre-processing transformations as densifying biomass feedstocks in many cases. Many studies suggest increasing the bulk density of biomass to produce a dense intermediate feedstock more easily and more economically transportable.[22] Transportation modes of lignocellulosic biomass include roads, railways, waterways, pipelines and integrated-modes.[18] Road transport is mainly used for short distances (<100 km), characterized by low fixed costs, high flexibility in terms of accessed sites but higher variable costs. On the other hand, railways, pipelines and waterways require significant fixed investment, stable flow of goods, incurring low variable costs and supplying large scale plants over long distances (>100 km). A possible solution for large-scale plants to take advantage of the high flexibility of road transport together with the low variable costs of rail or waterborne transportation is intermodal transportation that combines multiple transportation modes.[18,23] Finally, the suitable transportation system depends on the feedstock type form and quality, biorefinery plant capacity, storage and pretreatment technology, together with infrastructures, facility configurations, regulation, policy and environmental impacts; all these parameters should be considered in the modelling and optimization of the biomass supply chain.[18,24]

The development of a sustainable and efficient biomass logistic system may provide socio-economic benefits, creating innovative job networks and job opportunities in rural zones thanks to the valorization of their natural products.[19]

Among all the possible derivatives from LCB as raw material for potential substitution of petroleum-based fuels and derivatives, Levulinic acid (LA) and Levulinates (LEs) are ones of the most promising products.[25]

Identified as one of the top value-added platform chemicals issued from biomass by the National Renewable Energy Laboratory and the DOE,[25] LA can react with numerous functional groups due to its ketone carbonyl group and its acidic carboxyl group and to be transformed into many chemicals relevant for different market segments.

With a global market size of $27.2 million in 2019 ($28.3 million expected in 2020) and a compound annual growth rate (CAGR) of 8.8 % in the forecast period 2020-2030,[26,27] LA and its derivatives are intensely investigated since their applications extend in various industrial market sectors; pharmaceutical and cosmetic industries, agriculture and food industries, chemical, polymer and fuels industries.[9,28–39]

Levulinic esters (LEs) have peculiar physicochemical properties (similar to fatty acid methyl esters)[36], that can be adapted to both traditional chemical and process industry applications (e.g., solvents and additives for crude oil, flavoring, and fragrant agents and plasticizers[36] as well as new ones[40]). In addition, they are characterized by low toxicity, high stability, and high lubricity,[36] characteristics indicating the high potential of LEs as fuel additives. These characteristics make them promising in the panorama of sustainability as they are derived from “Renewable Feedstocks” and they bring a positive contribution to “Less Hazardous Chemical Syntheses”, “Safer Solvents and Auxiliaries”, and “Inherently Safer Chemistry for Accident Prevention” principles. Esters, as ethyl levulinate (EL) and butyl levulinate (BL), have been positively tested as oxygenate additives, showing an improvement of the lubricity, conductivity, freezing point and combustion emission of the fuel
into which they were blended.[32,41,42]

Table 1 Principles of Green Chemistry by Anastas and Warner.[16]

Lignocellulosic substrates comprising agricultural and forest residues, such as rice husk, sugarcane bagasse, and wheat straw, can lead to LA via carbohydrates hydrolysis.[28] In general, hydrolysis of LCB is carried out in an acid environment at high temperatures;[2] the hydrolysis processes will be widely discussed in the following sections.

Depending on the content of hexoses and/or pentoses in the initial substrate, LA is produced via the C6-sugars route or C5-sugars, as depicted in Fig. 2. In the hexoses path, the synthesis of LA is commonly obtained by the acid-catalyzed dehydration of C6-sugars to 5-hydroxymethylfurfural (HMF)[43], then hydrolyzed to LA. Homogeneous acid-catalysis is negative in terms of “Less Hazardous Chemical Syntheses”, “Safer Solvents and Auxiliaries”, “Inherently Safer Chemistry for Accident Prevention”, but positive as “Catalytic reagents (as selective as possible) are superior to stoichiometric reagents” according to the Green Chemistry Principles.

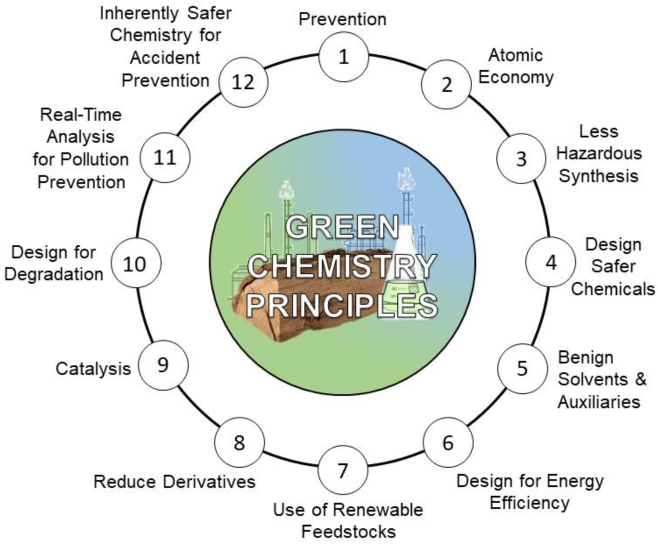

Fig. 1 Principles of Green Chemistry.[16]

Number	Principles	Description
1	Prevention	It relates to the prevention of waste generation. It is better to prevent waste than treat it after its generation.
2	Atomic economy	The synthetic methods should be designed to maximize the incorporation of all reactants into the final product, minimizing waste generation.
3	Less Hazardous Synthesis	Processes should be designed to use and generate safe and no-toxic substances. The replacement of toxic solvents is strongly recommended.
4	Design safer Chemicals	Chemicals should be designed to fulfil their functions but present the lowest toxic impact at the same time.
5	Benign Solvents & Auxiliaries	The use of solvents and auxiliaries should be avoided or at least considered safe substances.
6	Design for Energy Efficiency	Energy requirements should be considered to minimize the environmental and economic impact of the process; therefore, favour low temperature and pressure conditions.
7	Use of Renewable Feedstocks	Renewable raw materials should be preferred when they are economically and technically feasible.
8	Reduce Derivatives	Derivatives steps in the process should be avoided or minimized in order to not use other reactants and generate other waste.
9	Catalysis	The optimization of the synthesis method via catalysis should be preferred than the use of stoichiometric reagents.
10	Design for Degradation	The synthesis should produce substances intended to decompose into harmless products at the end of their function, without persisting in the environment.
11	Real-Time Analysis for Pollution Prevention	The production process should be monitored in real-time to avoid the formation of hazardous substances and possible accidents.
12	Inherently Safer Chemistry for Accident Prevention	Chemicals and process operating units should be chosen to minimize the possible occurrence of accidents, such as leaks, explosions and fires, and maximize occupational and environmental safety.

On the other hand, the C5-sugars route (mainly xylose) shows furfural, as the first hydrolysis intermediate, which is hydrogenated to furfuryl alcohol and hydrolyzed to LA. This way is less used because of the lower yield and the complexity of the additional processing steps.[37]

Routes to produce LEs are multiple:[29,33,44–46] from simple biomass-derived products like LA via esterification in an alcohol medium,[46] or furfuryl alcohol (process characterized by high yield and selectivity),[47] or 5-hydroxymethylfurfural and/or HMF intermediate ether in alcohol medium,[28,48] or directly from LCB (limited yield).[29]

The acid hydrolysis of either biomass-derived molecules, as sugar monomers, HMF, furfural, or direct LCB is characterized by by-products where humins are the main ones. Humins are carbonaceous, heterogeneous, polydisperse materials with a not well-known molecular structure,[55] constituted by furanic rings, and aldehydes, ketones and hydroxyls as main functional groups.[56] Produced in insoluble or partially soluble forms, humins are responsible for lower yields due to reagent consumption by degradation, and fouling of the reactor and catalyst, with poisoning effect for heterogeneous catalysts.[57]

Measures to mitigate the fouling effect, i.e. production and deposit of humins, could be applied, as lowering of lignocellulosic feedstock concentration or use of solvents which ensure humins dissolution, having severe economic effects in terms of equipment size and separation costs.[57]

The route entailing furfural hydrogenation is negative in terms of “Less Hazardous Chemical Syntheses”, “Safer Solvents and Auxiliaries”, “Inherently Safer Chemistry for Accident Prevention” and, for the C6 route, potentially less “Designed for Energy Efficiency”. Such aspects should be quantitatively studied using ad-hoc sustainability metrics able to rank the process alternatives.[49]

The synthesis of LA was first reported 150 years ago,[29] and this route was typically homogeneous acid-catalysed by mineral acids (e.g., HCl, H_2SO_4) at high temperatures and pressure (posing issues on “Inherently Safer Chemistry for Accident Prevention”). Even though characterized by high yields (Biofine process, 70-80 mol% yield),[50] it leads to difficult separation and recovery, equipment corrosion, and potential environmental pollution.[28] Therefore, recently, industrial production is more oriented to carry out heterogeneous acid-catalyzed processes (typically Brønsted acids, such as zeolites, ion exchange resins, etc.) because of good yields achieved and the simplicity of downstream processing.[28,29] Despite the insolubility of saccharide in alcohols, two routes are possible with glucose and fructose: transformation into 5-HMF and later into LA followed by final esterification or formation of its ether that finally

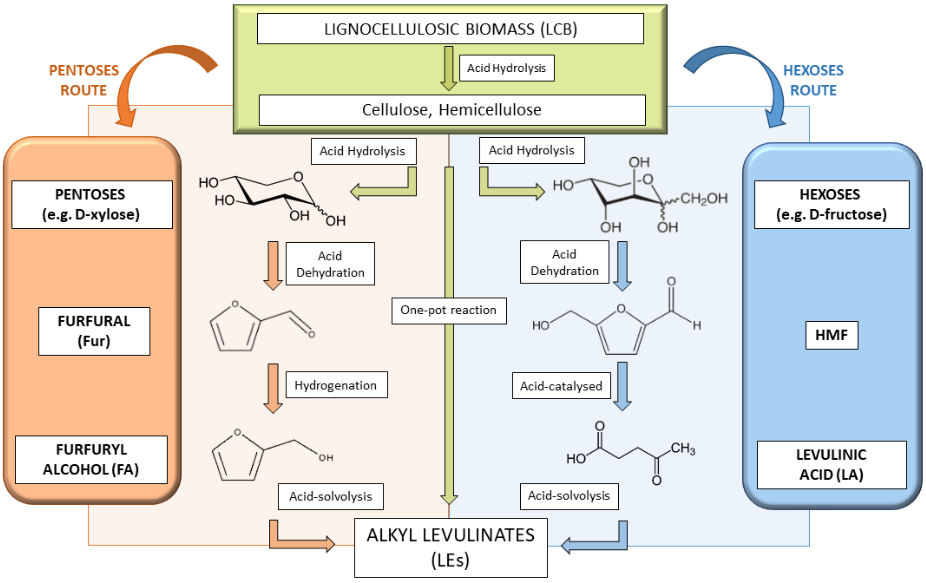

Fig. 2 Routes from lignocellulosic biomass (LCB) to levulinic acid (LA) and alkyl levulinates (ALs).

undergo dehydration or rehydration to the final levulinic ester, respectively.[29] Finally, the polysaccharides present in LCB (e.g., from hemicellulose, starch and inulin) can also be transformed into alkyl levulinates,[29] typically liquid acid catalyst systems, in the presence of alcohols, whereas the use of solid catalysts is less developed water.[29] Such solutions lead to improved “Inherently Safer Chemistry for Accident Prevention” characteristics.

In this review, various processes and different upstream and downstream processes for the production of LA and its esters have been examined, considering different starting substrates and precursors. Keeping in view the promising market potential of levulinates and their green-friendly-benefit uses, the review aspires to highlight the status quo of current industrial technologies in use and indicate the promising future laboratory technologies, upcoming to the scale-up.

2. Biomass feedstock pretreatments

Despite the final product target (i.e. a liquid biofuel or a platform chemical), the LCB must undergo a first step where the depolymerization of the polysaccharides occurs.[2] Whether the feedstock is a first or second-generation biomass, it can be depolymerized by hydrolysis or thermochemical processing. Due to the crystalline structure of cellulose and the lignin content, LCB needs to be pre-treated, before undergoing hydrolysis or thermochemical processes, to open its structure,[2,17] remove lignin in a reusable form,[51] decrystallize the cellulose fibers, reduce mass transport limitation for a biological or chemical catalyst to be used in successive steps to generate a high amount of sugars. Pre-treatments can be chemical (e.g., acid, alkaline, organic solvents, ionic liquids), physical and/or physicochemical (e.g., steam explosion, wet air, oxidation, ammonia fiber explosion,…), mechanical (e.g., grinding, chipping, milling,..), or biological (e.g., microbial, enzymatic) as shown in Fig. 3.[28] The choice of the best pre-treatment method is crucial for the product yield and also for the cost point of view, it could be more than 40 % of the total process cost.[52] This choice also has implications on the overall sustainability of the product obtained, having a direct impact (positive or negative) with respect to the Principles of Green chemistry, as displayed in Table 2. The mechanical treatments reduce the particle size, improve particle distribution, densification, the accessible surface area and porosity of the particles, i.e. improve mass transfer. Techniques such as milling, chipping, or grinding allow to mechanically transform the initial biomass without producing any secondary substances but are still considered expensive methods because of their high energy

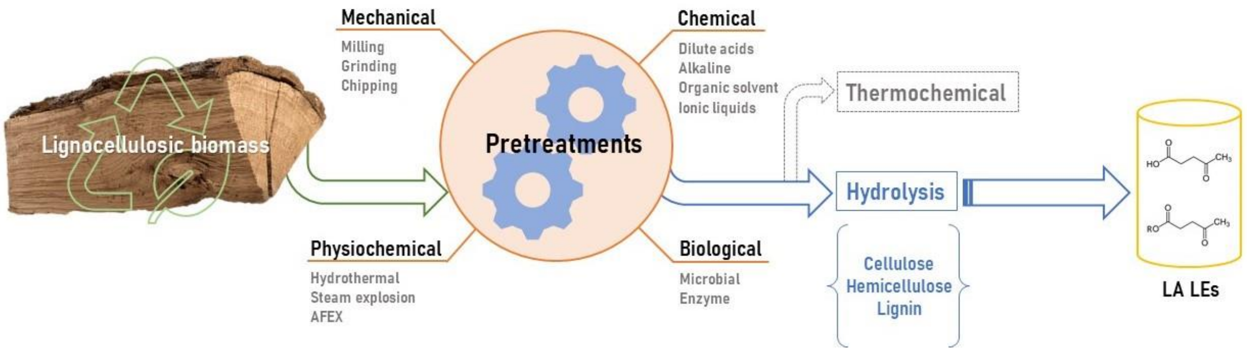

Fig. 3 Pre-Treatments methods and treatments for the primary conversion of lignocellulosic biomass (LCB).

demands.[53,54] One hand, mechanical pre-treatments allow to "Prevent" the formation of waste and minimize the potential for chemical accidents, including releases, explosions, and fires having a positive effect on the "Inherently Safer Chemistry for Accident Prevention" principle.

On the other hand, they cause a negative effect on the "Design for Energy Efficiency" principle and "Reduce Derivatives" principles. The chemical pre-treatments are more promising, usually less expensive, faster, and quite effective in degrading numerous complex-structured substrates. They include the use of diluted acids,[55,56] alkaline,[57] organic solvents,[58] ionic liquids.[59] Chemical pre-treatments enhance the substrate degradation and the availability of carbohydrates by removing lignin, decreasing the crystallinity of cellulosic components and the degree of its polymerization. Although highly efficient, the chemical techniques have some process limitations related to equipment corrosion, neutralization post-treatments and eco-toxicity.[60] From a sustainability stand point, those chemical pre-treatments requiring mild operating condition have a positive from a "Design for Energy Efficiency" stand point, but negative when considering the "Prevention", the "Safer Solvents and Auxiliaries ", the "Reduce Derivatives", and the "Less Hazardous Chemical Syntheses" Green Chemistry Principles. The physiochemical pre-treatments are based on treating the substrate with specific temperature, pressure condition and moisture content, making the different lignocellulosic components soluble and easily available for the next steps, improving the "Prevention" and "Atom Economy" aspects (being the latter the maximisation of the incorporation of all materials used in the process into the final product). Therefore, methods such as steam explosion,[61] hydrothermal,[62] and ammonia fiber explosion,[63] imply significant energy costs (i.e. negative effect on "Design for Energy Efficiency"), specific types of equipment, resulting in expensive and not very profitable on an industrial scale.[54] Biological pre-treatments are based on the employment of different microorganisms, like white and brown fungi used to depolymerize the lignin, cellulose and hemicellulose.[52] The microbial activity is due to the secretion of accessory enzymes (aryl alcohol oxidase, hydrolytic, glyoxyl oxidase, cellobiose dehydrogenase, copper oxidase enzymes), determining the simultaneous or selective radical degradation of the different part of the biomass.[54]

Table 2 Summary of Pre-Treatments methods lignocellulosic biomass (LCB).[52,53,60]

Pretreatment	Advantages	Limitations	Impact on Green Chemistry Principles[16]	
			Positive	Negative
Mechanical	Substrate particle size reduction and increased porosity (resulting in higher hydrolysis yield). Reduced cellulose crystallinity. Reduce reaction time, exposing more of the substrate.	High energy demand and highly energy inefficient operation. Have to be combined with other methods.	"Prevention" "Reduce Derivatives" "Inherently Safer Chemistry for Accident Prevention"	"Design for Energy Efficiency"
Chemical	Low cost (not for ionic liquid and organic solvent). Required mild operating condition. Low energy demanding. High reaction rate.	Not environmentally friendly (except readily biodegradable solvents). (Eco)Toxicity. Difficulty in recycling and reusing. Neutralization post-treatments for acid and alkaline methods. Demanding specific equipment anti-corrosion material.	"Design for Energy Efficiency"	"Prevention" "Safer Solvents and Auxiliaries " "Reduce Derivatives" "Less Hazardous Chemical Syntheses"
Physical/Physio-chemical	Modify the external and internal structure of biomass. Lower pretreatment severity.	High energy demand Specific equipment requirement.	"Prevention" "Atom Economy"	"Design for Energy Efficiency"
Biological	Low energy and operational cost demanding. More environmentally-friendly (low carbon footprint and high energy efficiency). Mild process conditions. No chemical addition.	Using specific microorganisms, adequate to the substrate. Difficult to control Low reaction rate, long process time. High space demanding (high capital cost).	"Inherently Safer Chemistry for Accident Prevention" "Safer Solvents and Auxiliaries" "Less Hazardous Chemical Syntheses" "Design for Energy Efficiency"	"Atom Economy"

From a sustainability point of view, the use of such methods improves aspects related to "Inherently Safer Chemistry for Accident Prevention", "Safer Solvents and Auxiliaries", "Less Hazardous Chemical Syntheses" and "Design for Energy

Efficiency”, having a negative effect on “Atom Economy”. Several factors affect the performance of the biological methods, as the type of microorganism used, incubation time and temperature, pH, inoculums concentration, moisture content and aeration rate, and being relatively time-consuming with slow reaction rate and requiring large space, they are often unattractive from the commercial point of view.[54,64]

Finally, the choice of adequate pre-treatment or combined-pre-treatments should be done considering that its cost should not affect the downstream processing steps and balance the trade-off with operational, capital, and biomass costs (Table 2). Thus, it should have low capital and operational cost: low energy demand, avoiding expensive materials and large size equipment due to the use of highly corrosive chemicals and high operating pressure conditions.[52,65]

3. Production routes to LA and LEs

3.1 Production from levulinic acid esterification

The simplest pathway to synthesize levulinic esters is the direct esterification of levulinic acid, using various acid catalysts and involving alcohols as reactants as well as solvents. Since the first attempts at synthesis using homogeneous acid catalysts in 1930s, such as HCl in excess of the corresponding alcohol,[66–68] the study of levulinic acid esterification has progressed towards the use of heterogeneous catalysts, due to their greater sustainability in terms of recyclability, regeneration, corrosivity and toxicity, reflecting some of the Principles of Green Chemistry such as “Prevention”, “Design for Degradation”, “Design for Energy Efficiency”. Using acid catalysts, the reaction mechanism considers the coordination of the carbonyl oxygen with the catalyst. Hence, carbonyl carbon positivity increases, leading to the formation of a carbocation. Then, the carbocation can react with the nucleophilic alcoholic group and eliminate the protonated hydroxyl group, releasing water and the specific levulinate ester (Fig.4).[69–71] Mineral acids, such as H_2SO_4, H_3PO_4, HCl, and p-toluene sulphonic acid (PTSA),[72] were strongly employed in the esterification for their high yields (>95 %)[73], fast reaction rates, and low cost, but their downstream drawbacks made it mandatory their replacement, even though there were some efforts to develop acid more sustainable as the bio-glycerol derived carbon sulfonic-acid.[74] Up to now, various heterogeneous catalysts, such as zeolites,[75–77] heteropolyacids,[78,79] acid ion exchange resins,[71,80,81] nano-structured solid acid,[82] sulfonic acid-functionalized organic polymer,[83] silica based,[84–86] metal oxide, zirconia based,[87] nano-material catalysts[88–91], ionic liquids[92] and biocatalysts[93–95] have been efficiently used to produce alkyl levulinates from LA (Table 3).

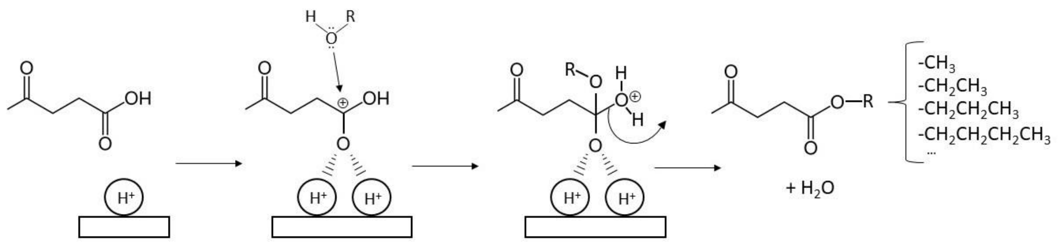

Fig. 4 Mechanism of acid catalysed levulinic acid esterification to levulinate esters.

Zeolites are widely used as solid acid catalysts and ion-exchangers in several processes thanks to the possibility of fine-tuning their properties. Micro/meso-HZ-5, modified and hierarchical H-ZSM-5 zeolite were tested to synthesize different levulinate esters obtaining yields above 90 %, operating at 120 °C up to 5 h and with the possibility of reusing the catalyst up to 7 runs.[75,96,97] In general, zeolites show high selectivity, even though the main challenges are thermal stability and mass transfer diffusion limitations. Heteropoly acids are obtained as a combination of specific metals (tungsten, vanadium or molybdenum). Used as homogeneous or heterogeneous catalyst depending on the structural composition, the heteropoly acid supported catalysts show better esterification conversion. Possible drawbacks are their thermal instability, low surface area, solubility in polar solvent, reusability and catalyst regeneration.[98] Using organic-salt of $H_4SiW_{12}O_{40}$, Luan et al.[78] produced ethyl levulinate and butyl levulinate with yields of 98.6 % and 96.5 %, respectively, for 5 h at reflux condition.[78] Similar yields have been obtained by Zhou et al.[99] in the production of butyl levulinate using ammonium co-doped phosphotungstic acid and silver co-doped phosphotungstic acid, reporting 99 % and 92 % for 2 h at 120 °C.[99]

For solid acid catalysts, various resins have been investigated in the study of levulinic acid esterification, such as Amberlyst-15, Amberlyst-46, Amberlyst-70, Purolite, Dowex and Aquivion. A key factor in their activity is the swelling property; this characteristic is related to the amount of divinylbenzene (cross-linking) that can affect the incrementation of pore size, i.e. improve the surface area and mass transfer.[71,80] For this reason, gel-type resins, as Dowex and Purolite, obtain better yields than macro-porous resins as Amberlyst, due to the greater swelling ability. Tejero et al.[71] investigated the esterification of levulinic acid by butanol over different resins, obtaining a yield around 64 % with Amberlyst-46 and yield of 93.5 % with Dowex 50Wx2. Ion resins can be easily separated from the product mixture, reused several times and prevent corrosion phenomena but at the same time they suffer from thermal-instability, disintegration at high temperature and in the presence of stirrer reactor; all these aspects combined with a high cost.[34,71,98]

Less expensive are silica-based catalysts; these inorganic porous catalysts have been widely studied for their proper surface functionalization, high and active surface area, chemical and thermal stability. They can be functionalized with various acid, such as $HClO_4$, H_2SO_4, PTSA, and incorporate different metal oxides.[84,85] Enumula et al.[85] analyzed the production of different levulinate esters using tungsten oxide incorporated SBA-16 catalyst obtaining yields up to 96 %.[85] In addition to high yields, silica based catalysts show high recyclability; perchloric acid decorated nano-porous silica offered until five esterification cycles to ethyl levulinate without any regeneration post-treatments.[84] Possible disadvantages to their use are the easy deactivation in polar solvents owing to H-bonding formation and the complexity and cost of their functionalization.[98,100]

Besides tungsten oxide, other metal oxides have received enormous attention as zirconium metal-oxide catalysts. Zirconia has been tested in various forms in the synthesis of levulinate esters, as simple form, silicon-doped zirconia, hybrid zirconia, organo-hybrid zirconia, showing better catalytic activity in the presence of hydrophobic groups, with alkyl levulinate yields of up to 99.9 %.[101] Furthermore, they are mechanically and thermally stable, non-corrosive, easy to regenerate, but they suffer from sulfated ions leaching and fouling.[98,100,102]

Some works also reported high yields by using ionic liquids as catalysts in levulinic acid esterification. One of the most active in the production of levulinates is the 1-Methylimidazolium hydrogen sulfate ([MIM][HSO$_4$]) with yields in propyl levulinate and butyl levulinate of 91 % and 92 %, respectively.[92] Ionic liquids have a bifunctional role: solvent and catalyst, thanks to their thermal stability, non-volatility, non-flammability and high ionic conductivity. Principal drawbacks are related to their viscosity, separation, recyclability, corrosiveness and high cost.[92,103]

Besides the catalyst choice, the selection of the solvent has a significant role in favouring an easy dissolution, mass transfer diffusion, and final products recovery, respecting the "Safer Solvent and Auxiliaries" principle. Alcohols are generally used as reactants and solvents. They are used in strongly excess to favor the acid esterification and decrease any reversible hydrolysis reaction.[71,72] Due to the low solubility of levulinic acid in non-polar solvents,[104] polar solvents as methyl tert-butyl ether, diethyl ether, and γ-valerolactone may be preferred. Some works also consider the use of ionic liquids[92] and supercritical carbon dioxide.[105,106]

The esterification can be carried out in different reactor systems: round bottom flask reactor with reflux condenser in order to avoid reactants and products evaporation;[80] stainless steel batch reactor, typically at high pressure by internal inert gas;[71] continuous flow reactor equipped with a fixed catalytic bed and flow control system;[85] reactive membrane reactor allowing simultaneous reaction and separation;[107] and supercritical fluid reactor, specific for fluid as supercritical carbon dioxide.[106]

Although the esterification of levulinic acid is a simple and effective route to produce levulinate esters, more promising production routes consider substrates and precursors further upstream in the LCB to levulinic acid/levulinic esters green chain.

Table 3 Production of levulinate esters from levulinic acid using various catalytic systems. ([c]yield after N reuse cycles tested without regeneration)

Substrate	Catalyst		Conditions[a]	Time	Yield[b]	Catalyst reuse[c]	Ref.
LA	Mineral acid	H_2SO_4	60 °C	3 h	91.2 % (EL)	-	108
			90 °C	24 h	100 % (BL)	-	108
			Reflux	16 h	100 % (EL)	-	109
LA	Organic acid	C-SO$_3$	Reflux	3 h	99 % (ML)	-	74
			Reflux	3 h	99 % (EL)	~ 99 % - 5 runs	74
		PTSA	120 °C	0.08 h	100 % (EL)	-	110
LA	Zeolite	Micro/Meso-HZ-5	120 °C	5 h	91 % (ML)	-	75
			120 °C	5 h	95 % (EL)	-	75
			120 °C	5 h	96 % (BL)	-	75
			120 °C	5 h	98 % (OL)	95 % - 6 runs	75
		Modified H-ZSM-5	120 °C	5 h	95 % (EL)	93 % - 6 runs	96
			130 °C	4 h	99 % (OL)	95 % - 6 runs	111
		Hierarchical H-ZSM-5	130 °C	5 h	97.2 % (HL)	~ 97 % - 6 runs	97

Table 3 (continued)

LA	Zeolite	H-BEA	120 °C	4 h	82.2 % (BL)	78.4 % - 5 runs	112
		H-MOR	120 °C	4 h	29.5 % (BL)	-	112
		H-Y	120 °C	4 h	32.2 % (BL)	-	112
		H-SM-5	120 °C	4 h	30.6 % (BL)	-	112
LA	Heteropolyacid	$H_4SiW_{12}O_{40}$	25 °C	8 h	90 % (EL)	-	113
			25 °C	8 h	92 % (ML)	-	113
			25 °C	8 h	90 % (PL)	-	113
			25 °C	8 h	91 % (BL)	-	113
		Organic salt of $H_4SiW_{12}O_{40}$	Reflux	5 h	98.6 % (EL)	90.5 % - 5 runs	78
			Reflux	5 h	100 % (ML)	-	78
			Reflux	5 h	87.8 % (IBL)	-	78
		Ammonium co-doped phosphotungstic acid	120 °C	2 h	99 % (BL)	~ 75 % - 4 runs	99
		Silver co-doped phosphotungstic acid	120 °C	2 h	92 % (BL)	-	99
LA	Ion exchange resins	Amberlyst 15	64.7 °C	5 h	82 % (ML)	75.3 % - 5 runs	80
			78.4 °C	5 h	71 % (EL)	-	80
			117.74 °C	5 h	55 % (BL)	-	80
		Dowex 50Wx2	80 °C	8 h	93.5 (BL)	-	71
		Purolite (CT224)	80 °C	8 h	90.5 % (BL)	-	71
LA	Silica	Tungsten oxide incorporated SBA-16	250 °C	10 h	96 % (ML)	-	85
			250 °C	10 h	95 % (EL)	80 % - 10 runs	85
			250 °C	10 h	94 % (PL)	-	85
			250 °C	10 h	94 % (BL)	-	85
		$HClO_4/SiO_2$	100 °C	5 h	99 % (EL)	90 % - 5 runs	84
			100 °C	5 h	90 % (BL)	-	84
LA	Zirconia	Mesoporous H_3PW_{12}/ZrO_2-Si(Ph)Si	Reflux	3 h	99.9 % (ML)	-	101
			Reflux	3 h	91.5 % (EL)	75 % - 3 runs	101
			Reflux	3 h	82.8 % (BL)	75 % - 3 runs	101
		Sulfated zirconia	70 °C	7 h	39.92 % (EL)	~ 39 % - 5 runs	107
		Super acid zirconia UDCaT-5	160 °C	3 h	100 % (ML)	95 % - 6 runs	87
			160 °C	3 h	100 % (EL)	-	87
			160 °C	3 h	95 % (PL)	-	87
			160 °C	3 h	98 % (BL)	-	87

Table 3 (continued)

LA	Nano-material catalyst	Sulphated TiO2 nano-composite	105 °C	3 h	90.4 % (EL)	60 % - 5 runs	88
			105 °C	3 h	75 % (EL)	-	88
		Organico-silica nanotube	65 °C	1.5 h	99.9 % (ML)	99 % -3 runs	89
		Iron-phosphonate nanoparticles	60 °C	2 h	98 % (ML)	90 % - 5 runs	90
LA	Carbonaceous catalyst	Sulphonated carbon	120 °C	9 h	88.2 % (EL)	76.8 % - 5 runs	114
			60 °C	1 h	91.5 % (EL)	-	115
		Carboncryogel crystal	78 °C	10 h	61.4 % (EL)	-	116
			150 °C	4 h	86.5 % (EL)	-	117
LA	Ionic liquid	[MIM][HSO$_4$]	90 °C	1.5 h	91 % (PL)	-	92
			90 °C	1.5 h	89.6 % (BL)	82 % - 6 runs	92
LA	Biocatalyst	CAL B lipase	45 °C	8 h	99 % (BL)	-	93

[a]using specific alcohol as solvent.[b]methyl (ML),ethyl (EL), butyl (BL), propyl (PL), hexyl (HL), octyl (OL) levulinate.

3.2 Production from precursors: 5-HMF, furfural and derivates

Derived-biomass precursors can be employed in the synthesis of LA and LEs. 5-Hydroxymethylfurfural (HMF) and Furfural (Fur), followed by their respective derivatives, have been identified as promising forerunners for the production of levulinates. Defined as a "sleeping giant" for its unrealized potential, HMF is a carbon-neutral feedstock and a good starting platform for fuels and chemicals (positive on "Use of Renewable Feedstocks"). Various raw materials have been employed for HMF synthesis, including aldose monosaccharides as glucose, galactose, sorbose and fructose. Proving the highest conversion, fructose has been selected as the best sugar in its production through dehydration in an acid-catalyzed reacting medium (positive on "Reduce Derivatives").[28,118] Production of HMF from glucose or fructose-glucose mixture is also the subject of various studies;[119–121] all of them agree on the significant catalytic complexity of the process (negative on " Catalysis"). Glucose is transformed into HMF through a first isomerization to fructose, then converted in a five-membered ring conformation (fructofuranose) and then undergone a series of three sequential dehydration to HMF,[122] requiring the presence of two different acid-catalytic activities: Lewis acidity for the isomerization and Brønsted acidity for the dehydration. Thus, fructose is typically privileged for better yields and lower process complexity (positive on "Less Hazardous Chemical Syntheses"), but, on the other hand, glucose is an attractive precursor due to its higher availability and lower cost[119,123] (better on "Design for Energy Efficiency"). Mineral acids, metal salts, and various solid acids have been employed over these years, emphasizing the most excellent efficiency of Brønsted-type catalysts (H_2SO_4, zeolites, ion exchange resins, etc.) converting fructose to HMF, compared with Lewis-acid catalysts.[124] Acid catalysis, mainly by Brønsted acids, is also required to transform 5-hydroxymethylfurfural into levulinic acid and its esters. While levulinic acid is produced by direct hydration of HMF under acid conditions, Quereshi's group[125] proposed a mechanism for the synthesis of alkyl levulinates based on two reaction pathways (Fig. 5): hydration of HMF to LA, which is esterified to its ester depending on the alcohol used for the alcoholysis, and/or HMF is converted to alkyl levulinates via HMF-ether intermediate, as via 5-ethoxymethylfurfural (EMF) for ethyl levulinate production[126] or 5-butoxymethylfurfural (BMF) for butyl levulinate.[127] Limited water content in the reacting mixture leads to favoring the second route in which 5-alcoxymethylfurfurals are major intermediates[125] instead of hydration to levulinic acid. Also in this case, a dedicated sustainability assessment should be carried out to quantify the comparison among the routes.

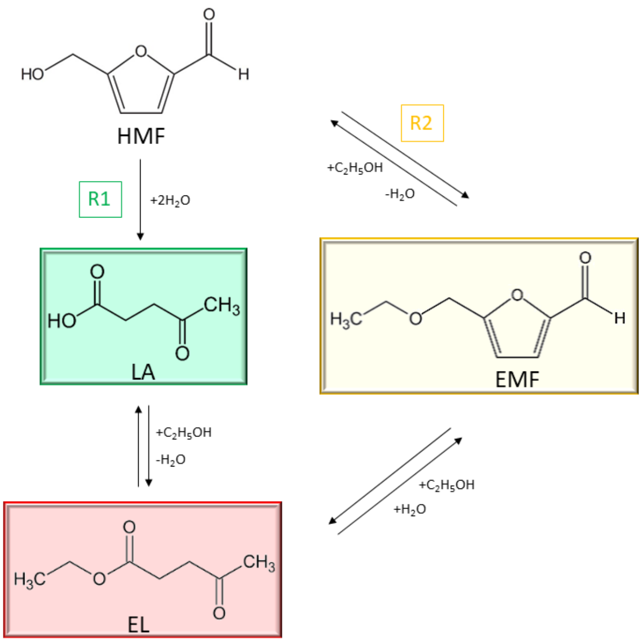

Fig. 5 Reaction scheme for the synthesis of Ethyl levulinate from HMF.

However, less explored than furan and cellulose as feedstock for the synthesis of levulinates,[125] solvolysis of HMF has been tested with various acid-catalysts, mainly heterogeneous (Table 4), such as zeolites,[128,129] zirconia, sulfated zirconia, mesoporous silica,[129] heteropolyacid,[126] ion exchange resins,[130] and ionic liquids.[131]

Even though in the presence of a complete HMF conversion, literature experiment data measure low yields of levulinic esters and acid (low intensified process). For instance, some of the highest yields in ethyl levulinate was achieved by Wang et al.[132] yield of 81 % by using modified MOFs-derived carbon material catalyst,[132] Chithra and Darbha with 85.5 % using MZSM-5 zeolite,[133] and Srinivasa rao et al. 92 % with titanium exchanged heteropoly tungstate catalysts.[134]

Higher alkyl levulinate yields are achieved starting from furfuryl alcohol (FA). Neves and her group[135] considered that due to a higher efficient theoretical carbon atom for the FA-to-alkyl levulinate system than for the HMF-to-alkyl levulinate, and lower production of by-products.[125] Humins are also inevitably produced from the degradation of HMF and furfural in an acidic environment, leading to limitations on the catalytic activity and efficiency of downstream processes[128,136] (negative effect on “Reduce Derivatives”). In addition to the use of special solvents to ensure its complete solubilization and prevent fouling and deactivation of the catalyst[137] (negative effect on “Safer Solvents and Auxiliaries”), oxygen has been tested as a possible suppressor of the formation of humins and promoter of the selectivity to desired products (positive effect on “Catalysis”). Wang and his group studied the production of methyl levulinate from HMF, catalyzed by zeolite, in the presence of oxygen; it resulted in a phenomenon of humins removal via oxidative species formed at high temperatures (up to 150 °C), compared to nitrogen in the same conditions.[128]

Furthermore, the employment of inefficient technologies might lead to hotspots or/and non-uniformity of reacting temperature, facilitating the formation of by-products, with effects on “Inherently Safer Chemistry for Accident Prevention”. Microwave-assisted heating has several advantages in rapid and homogeneous heating, reduced time-contact and higher product yield,[138] being promising from “Inherently Safer Chemistry for Accident Prevention” point of view. Although tested on a laboratory scale, Microwave reactors are complex to scale-up, and, thus, any of them have been employed yet for large-scale production of alkyl levulinates.[125] Quereshi and his group compared ethyl levulinate production from HMF, catalyzed by metal salts, via microwaves and non-microwave instant heating. They demonstrated that the non-microwave instant heating can be a promising alternative to microwave technology, leading to comparable results, more accessible to scale-up and, thus, more accepted in the industrial market.[125] The scale-up is also favored by using a continuous flow production system, which allows greater control of the process parameters but is still scarce investigated in the literature related to HMF upgrading to levulinic acid and esters.

Table 4 Literature data on catalytic conversion of HMF to LA and LEs.

Substrate	Catalyst		Conditions[a]	Time	Conversion HMF	Yield[b]	Catalyst reuse[c]	Ref.
HMF	Mesoporous silica	SO$_3$H-SBA-15	140C °C	24 h	99 %	75 % (EL)	~ 75 % - 3 runs	129
HMF	Metal salts	CuCl2	160 °C Microwaves	5 min	93.4 %	47.5 % (EL)	-	125
		FeCl$_3$	160 °C Microwaves	5 min	73.9 %	43.2 % (EL)	-	125
HMF	Zeolite	H-beta40	170 °C (under O$_2$)	50 min	100 %	69.6 % (ML)	50 % - 3 runs	128
		MZSM-5	150 °C Ethanol/Hexan	12 h	94.2 %	85.5 % (EL)	-	133
HMF	MOF-based heteropolyacid	[Cu-BTC][HPM]	140 °C	12 h	100 %	20.2 % (EL)	~ 20 % - 5 runs	126
HMF	Heteropoly tungstate cat.	Ti$_{0.75}$TPA	120 °C	6 h	100 %	92 % (EL)	-	134
HMF	Resins	Amberlyst 15	100 °C	24 h	95 %	17 % (EL)	-	130
		Amberlyst 70	160 °C	2 h	-	61.7/11.9 % (EL/LA)	-	139
HMF	Sulfonic-acid-funct. carbon cat.	C-SO$_3$H	140 °C	8 h	100 %	81 % (EL)	61 % - 5 runs	132

[a]using water or alcohols as solvent, unless otherwise specified.[b] Methyl (ML), ethyl (EL) levulinate.[c] yield after N reuse cycles without regeneration.

Key element in the pentoses-route from LCB, furfural is a pivotal intermediate for many bio-based chemicals, including for LA and its esters. This furanic aldehyde is synthesized mainly from hemicellulose-derived pentoses such as xylose and arabinose through acid-catalyzed dehydration.[118,140] Traditionally, the transformation of hemicellulose is realized via chemical catalytic or physico-chemical processes, since the biological methods are inefficient, and xylose, a significant component of hemicellulose (69,7 - 88,6 relative w/w%)[141] is acid-dehydrated by mineral acids as catalysts. Due to several limitations of the traditional furfural production such as high energy demand, corrosion, ecotoxicity and low furfural stability in acid medium, alternative processes have been considered, employing novel catalysts coupled with more effective and sustainable solvents.[142] Numerous homogeneous and heterogeneous catalysts have been tested (Table 5), such as solid acids,[143] oxides,[144,145] metal chlorides,[146] zeolites[147] and ion exchange resins,[148] demonstrating high furfural yield (up to 90 % starting from xylose) and excellent efficiency. Some of them coupled with biomass-derived organic solvents such as γ-valerolactone (GVL) in single-phase liquid or biphasic water/GVL systems, resulting positively in the absence of insoluble humins.[140,142,148,149] The production of humins is one of the significant limitations in the conversion to LEs by furfural and HMF, leading to the loss of substrate, catalyst fouling, deactivation and problematic separation post-treatments.[128] Furfural can be converted into levulinic acid and esters via multiple steps (Fig. 6), involving the partial hydrogenation of furfural to furfuryl alcohol in gas or liquid phase and following by the acid-catalyzed conversion of furfuryl alcohol into levulinic acid or ester in the liquid phase, respectively aqueous or alcoholic.[135,150–153] Although the pentoses route to furfural has been deployed on an industrial scale for decades, the subsequent hydrogenation to FA and production of LEs are still being studied and in development. Firstly, the catalytic hydrogenation of furfural leads to various downstream products, including furfuryl alcohol, through to the employing of different kinds of materials, among non-noble metals (Ni, Co, Zr, etc.)[154–156] and noble metals (Ru, Pt, Pd, etc.)[157–159] based catalysts. High furfuryl alcohol yield and selectivity (up to 99 %) can be achieved by the control and the fine-tuning of reaction conditions: temperature, high or mild temperature condition depending on the catalyst; H_2 pressure, typically high for deeper hydrogenation; time, longer times lead to higher hydrogenation yields; solvents and catalyst, mono-metallic or synergistically coupled with a second metal or specific support.[160] The need for hydrogenation catalysts, high-pressure conditions and the use of hydrogen as a reactant make this first intermediate step on the production of levulinates from furfural cost demanding and unfavoured in terms of process safety. A potential solution to the direct use of molecular hydrogen is the transfer hydrogenation (TH); this reaction reduces targeted functional groups through hydrogen transferred from a donor species without the employment of molecular hydrogen.[161] Recently, this technique has been applied in synthesizing alkyl levulinates (e.g., isopropyl levulinate and ethyl levulinate) from furfural via furfuryl alcohol in the presence of a hydrogen-donor solvent and a catalyst with bifunctional activity: hydrogen transfer to furfural and acid-solvolysis of furfuryl alcohol.[152,162] Zr/SBA-15 has been tested in a one-pot conversion of furfural into methyl levulinate by using near-critical methanol as hydrogen donor reporting a yield of 36.3 %.[163] Noble metals have also been tested, reporting promising results as 80.2 % yield in isopropyl levulinate with $Au–H_4SiW_{12}O_{40}/ZrO_2$ in mild condition.[153] Although very active, the use of expensive noble metals is not economically attractive. Peng et al. combined simpler and more cost-effective catalysts: Zr-MCM-41 catalyst and Amberlyst-15 obtaining a yield of 85.3 % comparable to the ones via noble metals catalysts.[164] Through a different mechanism, furfural can also be converted in levulinic acid/esters via HMF and subsequence esterification of levulinic acid in the presence of alcohol, being furfural convertible into HMF by adding a hydroxymethyl group to the furan ring in the presence of electrophilic species.[139] Applicable directly to xylose, this reaction not only avoids the hydrogenation step but also allows pentose sugars and/or furfural to be processed by only acid catalysis, as in the hexose route, enhancing the efficiency for the production of levulinic acid/ester from LCB.[139]

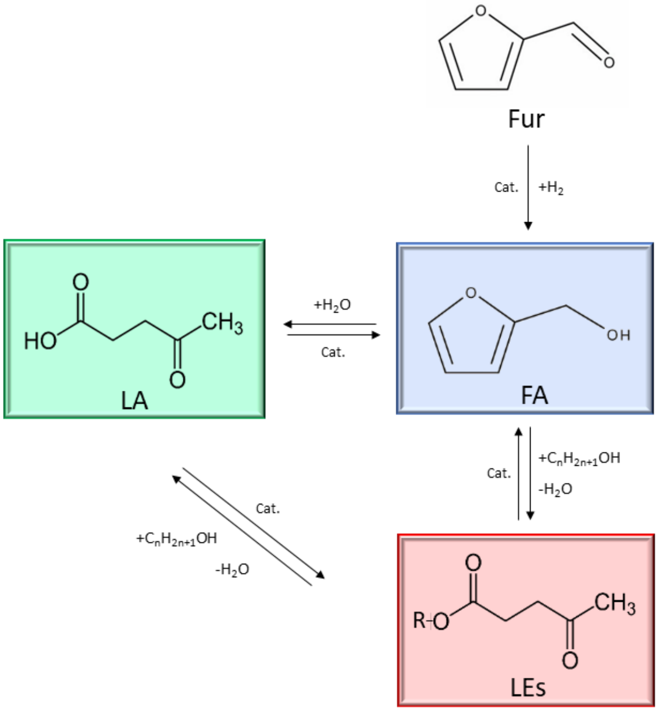

Fig. 6 Reaction scheme for the synthesis of Levulinate esters from Furfural.

Subsequent to hydrogenation, the alcoholysis of furfuryl alcohol to levulinic products occurs in two acid-catalyzed steps: furfuryl alcohol reacts rapidly to form intermediates, mainly 2-alcoxymethylfurane,[151] in the presence of alcohol (or water), which are converted then into levulinic ester/acid.[47,151] Being not fully exploited and oversupplied in the chemical market (about 65 % of the overall use of furfural to produce FA),[165,166] several studies have aimed to develop a feasible and competitive pathway for reforming and upgrade FA.[165,167] The alcoholysis via acid catalysts represents a convenient and atom-economic route to obtained value-added alkyl levulinates.[168] Besides sulfuric acid and other acids,[47,150] various homogeneous and heterogeneous catalysts have been investigated such as zeolites,[151,169] sulfonic acid ion-exchange resins,[151,170,171] organo-silica nanotubes,[172] oxides,[173] salts,[174] and porous aluminosilicate acid catalysts[135] (Table 6); generally operating at temperatures range between 110-140 °C and pressure up to 20 bar to avoid to operate below the boiling point of the reagents.[175] Even though mineral acids are still favored for their low cost and high availability, heterogeneous catalysts are gaining a foothold in the industry, avoiding corrosion effects, limiting downstream steps and ecotoxicity, all with the same efficiency.[176] The overall furfural-via-furfuryl-alcohol process allows to achieve yields in LA in the range 83-93 mol%,[177] and yields in levulinic esters around 95-98 mol%.[176] Nevertheless, this solution is less inherently safe.

Table 5 Literature data on catalytic conversion of furfural in levulinic acid (LA) and LEs.

Substrate	Catalyst		Conditions[a]	Time	Conversion Subst.	Yield[b]	Catalyst reuse[c]	Ref.
Furfural	Oxide	Nb_2O_5-ZrO_2	180 °C	8 h	92.6 %	66.5 % (IPL)	19.7 % - 3 runs	152
		Cu/Nb^2O_5	160 °C	3 h	92.7 %	67 % (LA)	55.2 % - 4 runs	178
Furfural	Silica based cat.	Zr/SBA-15	270 °C	10 h	100 %	36.3 % (ML)	32 % - 5 runs	163
		Zr-Al/SBA-15	180 °C	3 h	92.8 %	66.3 % (EL)	51 % - 4 runs	179
			180 °C	3 h	98.8 %	19.3 % (PL)	-	179
			180 °C	3 h	97.5 %	69.7 % (BL)	-	179
Furfural	Silica based/ Zeolite	Zr/SBA-15, ZSM-5	180 °C	8 h	100 %	55 % (EL)	-	162
Furfural	Modified zeolite	$(Sn)_{SSIE}$beta 1	120 °C	24 h	95 %	11 % (2-BL)	-	180
		$(Zr)_{SSIE}$beta 1	120 °C	24 h	98 %	17 % (2-BL)	-	181
Furfural	Zeolite/Resins	Zr-MCM-41 Amberlyst-15	130 °C	24 h	98.8 %	85.3 % (PL)	18.2 % - 5 runs	164
Furfural	Ion exchange resins	Amberlyst 70	160 °C DMM/water	2 h	96.2 %	26.5 % (ML+LA)	-	139
		Amberlyst 70	160 °C DMM/methanol	2 h	89.3 %	46.8 % (ML+LA)	-	139
		Amberlyst 70	160 °C DMM	2 h	98.9 %	30 % (ML+LA)	-	139
Furfural	Acidic resin	D008	190 °C DMM/methanol	1 h	71.6 %	39.1 % (ML+LA)	-	182
Furfural	Nanoparticles supported	Pt/$ZrNbPO_4$	130 °C	6 h	92.28 %	69.8 % (EL)	57 % - 5 runs	183
		Ir/$ZrNbPO_4$	130 °C	6 h	95.7 %	55.2 % (EL)	-	183
Furfural	Modified mesoporous	SO_3H@Ni−A	120 °C	1.6 h	100 %	98.6 % (ML)	-	184
			120 °C	1.6 h	100 %	97.2 % (EL)	~ 97 % - 20 runs	184
			120 °C	1.6 h	100 %	85.3 % (PL)	-	184
			120 °C	1.6 h	100 %	72.7 % (BL)	-	184
Furfural	Noble metal	Au−$H_4SiW_{12}O_{40}$/ZrO_2	120 °C	24 h	100 %	80.2 % (IPL)	~80 % - 5 runs	153
Furfural	Heteropolyacid	$H_3PW_{12}O_{40}$/SiO_2	170 °C	12 h	-	51 % (LA)	~50 % - 3 runs	185

[a]using water or alcohols as solvent, unless otherwise specified. [b] Methyl (ML), ethyl (EL), propyl (PL), butyl (BL) levulinate. [c]yield after N reuse cycles tested without regeneration.

Table 6 Literature data on catalytic conversion of furfuryl alcohol (FA) in levulinic acid (LA) and LEs.

Substrate	Catalyst		Conditions[a]	Time	Conversion Subst.	Yield[b]	Catalyst reuse[d]	Ref.
FA	Mineral acid	H_2SO_4	125 °C	3 h	100 %	72 % (LA)	-	150
			110 °C Butanol/water	10 h	100 %	97 % (BL)	-	186
FA	Mixed-acid cat.	$CrCl_3/H_3PO_4$	130 °C	8 h	99 %	95 % (BL)	-	187
FA	Aluminium salt	$AlCl_3$	123 °C	2.7 h	100 %	95.7 % (EL)	94.5 % - 6 runs	188
FA	Ion exchange resins	Amberlyst 70	110 °C	6.5 h	100 %	99 % (BL)	-	151
FA		Ambelyst 35	110 °C	6.5 h	100 %	93 % (BL)	-	151
FA		Ambelyst 15	140 °C	24 h	100 %	90 % (EL)	75 % - 3 runs	135
FA	Zeolites	ZSM-5	125 °C	3 h	100 %	45 % (LA)	-	150
FA		HZSM-5	110 °C	6 h	100 %	40 % (BL)	-	151
FA		HZSM-5	170 °C	-[c]	-	80 % (ML)	-	175
FA		HZSM-5	170 °C	-[c]	-	59 % (EL)	-	175
FA		HZSM-5	170 °C	-[c]	-	60 % (n-PL)	-	175
FA		H-ferrierite	110 °C	6 h	100 %	12 % (BL)	-	151
FA		H-Beta	140 °C	24 h	100 %	60 % (EL)	-	135
FA		H-MCM-22	140 °C	24 h	100 %	47 % (EL)	-	135
FA	Mesoporous aluminosilic.	Al-TUD-1	140 °C	24 h	100 %	80 % (EL)	50 % - 3 runs	135
FA		Beta/TUD-1	140 °C	24 h	100 %	63 % (EL)	-	135
FA	Mesoporous silica	SBA-15-SO_3H	110 °C	4 h	100 %	96 % (BL)	-	151
		Ti-KIT-6	110 °C	5 h	94 %	94 % (BL)	88 % - 5 runs	189
FA	Mesoporous carbon	ArSO_3H-HMCSs	120 °C	2 h	100 %	81.3 % (EL)	~ 80 % - 10 runs	190
FA	Sulfated zirconia	1M-SZF Magnetical. separable	120 °C	2 h	100 %	96 % (EL)	87.8 % - 8 runs	191
FA	Sulfonic acid functionalized	p-TSA	Reflux	6 h	100 %	96 % (EL)	~ 96 % - 5 runs	192
			Reflux	6 h	100 %	97 % (BL)	-	192
FA	Indium based	In(OTf)$_3$	Reflux	1.5 h	-	92 % (BL)	-	193
			Reflux	3 h	-	83 % (PL)	-	193
FA	Nanomaterial	Al/DFNS/Pr-SO_3H	140 °C	4 h	100 %	93.5 % (HL)	85.7 % - 4 runs	194
FA	Supported Heteropoly acid	Sn$_1$-TPA/K-10	110 °C	5 h	100 %	98.4 % (BL)	93.6 % - 5 runs	195
		Zn$_1$TPA/Nb_2O_5	110 °C	5 h	100 %	94 % (BL)	90 % - 4 runs	196
		TPA/SBA-16	110 °C	3 h	100 %	97 % (BL)	84 % - 4 runs	197

[a]using water or alcohols as solvent, unless otherwise specified. [b] Methyl (ML), ethyl (EL), propyl (PL), butyl (BL), hexyl (HL) levulinate.[c]continuous reactor.[d] yield after N reuse cycles tested without regeneration.

Although very appealing, the pentoses route, mainly the furfural pathway, is still too limiting by the excessive formation of by-products, variety and cost of feedstocks and high cost of precursors as furfural; furfural price ranged between \$800/t and \$1600/t in 2006-2016 and increased to \$2700/t in 2017[198] and furfuryl alcohol price is \$1500/t or even higher.[199] Therefore, the high cost of these precursors makes the production of levulinic products via the pentoses route too economically unattractive than via hexoses.

Most biomass conversion processes into chemical platforms are in batch systems, as they are mainly based on chemical or biological technologies.[160,200] The industrial production of precursors, such as furfural, HMF, and final products, is a well-consolidated batch technology. However, several research groups have highlighted the evident benefits of continuous-flow biomass conversion processes.[160,200,201]

Compared to batch processes, continuous processes provide:

- Enhanced control of reaction conditions. Better tuning and flexibility of process variables, especially in the presence of consecutive reactions and intermediates.
- Facilitating the process scale-up. Most of the processes about biomass valorization are still on the laboratory scale, mainly batch, and potentially industrialized by being turned into a continuous process.
- Major process intensification. Biomass processes are typically complex multi-steps; continuous flow technologies lead to the escalation of the process, simplifying the reaction and the downstream steps, as catalyst re-generation.
- Process safety. Biomass processes often require the removal of oxygen, which is released in the form of H_2O and/or COx, resulting potentially in the increasing of pressure in batch systems and, thus, in new and uncontrolled processes. The continuous flow process allows removing oxygen without interfering with the reacting conditions.

The advantages of continuous flow processes have been investigated deeply related to the furfural pathway: Audemar and his group compared the heterogeneously catalysed conversion of furfural to furfuryl alcohol in batch and continuous reactor. They demonstrated that a continuous flow reactor can be a solution in the case of catalyst poisoning as it is characterized by a shorter contact time between catalyst and reactive species (in this case furan molecules) than the batch process, prolonging the activity of the catalyst, its stability and increasing the space-time yield.[202] Following these results, Wang's group remarked how further efforts should be done to scale-up furfural valorization and challenges for continuous technologies, also in laboratory scale, as needing of specific dedicated equipment for continuous dosing, connections, etc.; defining of procedure for start-up and shutdown steps; storing safely reactive materials.[160] Alcoholysis of furfuryl alcohol to alkyl levulinates in a continuous system was investigated by Zhao and his group.[175] Comparing a closed pressure-controlled batch vessel and a continuous catalytic bed packed reactor, they reported an increase in the final yield of levulinate ester, particularly promising for methyl levulinate whose yield increased by 11-15 % compared to the batch case. Therefore, research into innovative processes for converting precursors using continuous mode is crucial in intensifying these processes and their development on an industrial scale.[203]

3.3 Production from glucose/fructose or sugar monomer

Monosaccharides are the basic unit of carbohydrate molecules hydrolysable from LCB, such as disaccharides and polysaccharides. Among these, hexose sugars are the most commonly occurring monosaccharides, mainly including glucose and fructose, and more simply used as precursor molecules to synthesize of LA or LEs.[204] The reaction of dehydration of C6 sugar to HMF and further rehydration and ring-opening of HMF to LA or LEs have attracted lots of research in reaction mechanism and system design to gain insight into this process. Table 7 shows the conversion of hexose monosaccharides to LA and LEs by different catalysts and under different conditions. Because of its greater abundance in cellulose and hemicellulose and consequently its lower cost, glucose is preferred over fructose. Nevertheless, fructose gives a higher yield in levulinate products than glucose, due to its greater molecular instability, which leads to easier opening of the ring structure. Indeed, glucose needs to be isomerized to fructose and then further dehydrated to HMF and rehydrated to LA (Fig. 7).[205] The mechanism difference between the

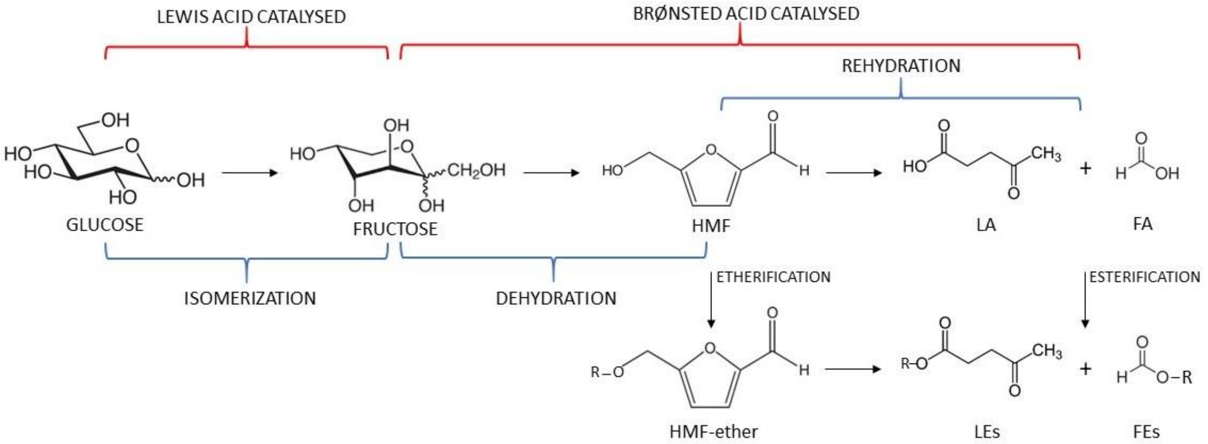

Fig. 7 Reaction scheme of conversion of glucose to LA and LEs.

production of LA and LEs is the formation of an alkylated intermediate, such as 5-(ethoxymethyl)furfural for ethyl levulinate case, and co-products as formic acid esters. Over the past decade, numerous studies have tested both homogeneous and heterogeneous catalysts in the LA and LEs production from C6 and sugar. The easy contact with the substrate, combined with the low cost, make the homogeneous acid catalyst, as H_2SO_4, HCl, HNO_3, and H_3PO_4 the subject of various studies about the production of levulinic acid and alkyl levulinates via solvolysis. The use of H_2SO_4 with different monosaccharide substrates, such as glucose,[206,207] and fructose,[199] have reported promising results in terms of LA yields, always taking into account its corrosive and pollutant effects. Other homogeneous acids, as HCl, trifluoroacetic acid (TFA), and PTSA, have been also tested in LA production. Heeres et al. reported a LA yield of 35 % from glucose and of 45 % from fructose by using TFA;[208] LA yield of 16 % from fructose hydrolysis with PTSA;[207] and Brasholz et al. tested HCl obtaining a LA yield of 72 % from fructose.[209] Transition metal chlorides, especially $CrCl_3$, have been coupled with mineral acids, affecting the conversion of glucose positively to LA due to their key role in the isomerization of glucose to fructose.[210,211] However, this Lewis acid catalyst also promoted the overall conversion rate of glucose when combining with Brønsted acid HCl for further rehydration of HMF, resulting in side reactions and by-products. Optimization of both concentrations of Lewis acid and Brønsted acid in this cascade reactions should be done to maximize the desired product yield,[211] i.e. improving simultaneously two principles of the Green Chemistry, namely "Catalysts" and "Reduce Derivatives". A fine-tuning Lewis/Brønsted acid activities using this metal chloride was presented by Ya'aini et al.;[212] developing a hybrid catalyst ($CrCl_3$/HY) and using central composite design (CCD) under the response surface methodology (RSM) for LA production, 47 wt% yields of LA-based on hexoses content was obtained at 145.2 ^oC and 147 min.[212] Not limited to typical batch systems, homogeneous acid catalysts have also been applied in the continuous flow process for different products, including 5-(chloromethyl)-furfural (CMF), HMF and LA from carbohydrates such as sucrose, glucose and fructose. A mixture with 2M HCl aqueous-methanol (v:v=1:2) was inserted into a continuous flow reactor and gave 46 wt% yield of LA under 140 ^oC and 80 min after filtering insoluble by-products.[209] The industrial application should always be supported by the maximization of Green Chemistry Principles such as "Less Hazardous Chemical Syntheses", "Safer Solvents and Auxiliaries", "Design for Energy Efficiency", "Reduce Derivatives" and "Inherently Safer Chemistry for Accident Prevention". Although homogeneous catalysts are used on a large scale, the conversion of monosaccharides to LA in heterogeneous catalysis has attracted extensive attention in recent years, due to their easier recovery, environmental benign properties. Futhermore heterogeneous catalysts may provide an efficient methodology with higher selectivity to LA and reaction rates.[117] Heterogeneous catalysts such as zeolites,[213] acid resins and polymers,[214–216] metal oxides,[217] heteropoly acids[218] have been tested, obtaining up to LA yields exceeding 70 %. These same classes of acid catalysts have also been studied in the production of alkyl levulinate from C6 monosaccharides, being the reaction mechanism similar to that of its precursor acid. Besides the use of single Brønsted acid catalysts, as reported by Xu et al.[219] for the production of ethyl levulinate via zeolites, or by Kuo et al.[220] for the synthesis of methyl levulinate via titanium oxide nanoparticles, several researchers investigated the synergic combination of Lewis-Brønsted catalysts in fructose alcoholysis. Glucose isomeration to fructose represents the rate-limiting step of biomass conversion to levulinates. Thus, using a dual-activity catalyst[221] or coupling a Lewis acid catalyst, which is considered to act as isomeration catalyst, with a Brønsted catalyst, responsible for the alcoholysis, the selectivity to alkyl levulinate is strongly favoured. Metal salts have been deeply analysed for this purpose, since they can act as Lewis catalysts and they are commonly stable, recyclable and inexpensive. Zhou et al. studied the use of $Al_2(SO_4)_3$ as single catalyst in methanolysis of glucose. Obtaining a ML yield of 64 % at 160 °C, this catalyst showed to provide Lewis and Brønsted sites through Al^{3+} ions.[221] Al^{3+} ions have been studied also by Liu et al.[222], coupled with montmorillonite catalysts. In this case, the catalyst determined a ML yield of 60 %, with the possibility of recycling up to 5 times.[222] Lewis acidic activity can also be achieved by using metal oxides. Heda et al. highlighted the synthesis of EL from glucose by the combination of H-USY zeolite and metal oxides as TiO_2, ZrO_2 and SnO_2.[223] The highest EL yield have been resulted from the combination with SnO_2 which increases the yield up to 81 %, by increasing the rate of isomerisation and the solubility of glucose in ethanol.[223] Improving the overall reaction rates, higher glucose concentration may be handled, following the green chemistry principles such as utilization of renewable materials and omission of derivatization steps and output-led design.[223] In any case, the choice of developing a "high-gravity" process must consider the increase in monosaccharide concentration as being directly related to the increase in possible undesirable reactions, such as the production of the by-product humins.[203] One of the advantages of glucose alcoholysis, reported by Hu et al.,[224] is that the alkylated intermediate formed in alcohol can suppress the formation of humins. The alkyl group can protect the reactive intermediate and enhance the production of LA esters. Their group also identified this advantage of using alcohol for one-pot synthesis of LEs from xylose.[225] Despite this advantage, it is worth noticing that intermolecular dehydration of alcohols to ethers was significant in the alcoholysis reactions, which can hinder the scale-up of this process,[226] having a negative effect also on the "Inherently Safer Chemistry for Accident Prevention", and "Safer Solvents and Auxiliaries".

Among the literature listed in Table 7, the highest yield values of alkyl levulinate are obtained from fructose alcoholysis. Liu et al.[227] reported a maximum 84 mol% yield of ethyl levulinate, obtained at 120 ^oC for 24 h through different sulfonic acid-functionalized carbon nanotubes catalyzing fructose dehydration to ethyl levulinate.[227] A linear relationship between catalytic activity and acid density of the catalyst was found and this catalyst showed its facile separation, high thermal stability, and ease of recovery. High catalytic activity and good thermal

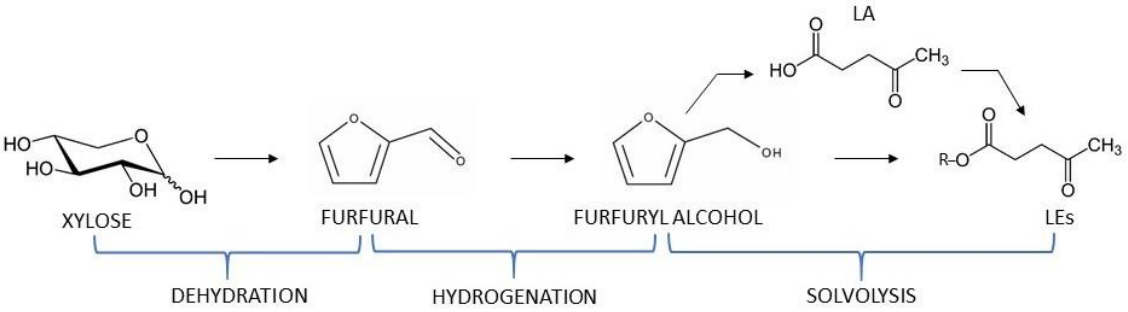

Fig. 8 Reaction scheme of conversion of xylose to LA and LEs.

stability over other solid catalysts have been demonstred by metal oxides. Oprescu et al.[228] investigated the production of methyl levulinate from fructose by using TiO_2-La_2O_3 mixed oxides on solid Fe_3O_4 nanoparticles. Fructose conversion was complete with a ML yield of 95 %, and the catslyst and reusability of the catalyst showed a decreasing by almost 10 % after five cycles without any regeneration.[228] Xu et al. studied the synthesis of ML via sulfated montmorillonite (SO_4^{2-}/MMT), reporting a yield of 65 %. They reported a 36 % reduction in yield after the third run without regeneration, showing that, unlike metal oxides, solid sulfated catalysts suffer from instability due to the easy loss of the sulfate group. Acid resins are also highly active, but regeneration of the catalyst is necessary to preserve their activity. Ramirez et al.[127] studied the fructose butanolysis over both gel-type and macroreticular sulfonic PS-DVB resins. The catalyst screening showed that gel-type resins tend to swell highly, having a less acid site density in the swollen state and resulting in the most effective activity in term of BL yield (73.4 %). The yield decreased by 22 % after 3 cycles due to the loss of active sites and the formation of polymers (solid humins) covering the resin during the reaction.[127] Dehydration of C6 sugar to LA and LEs consists of several reaction steps; to better understand this system, it is necessary to consider all of the different parameters that can affect the final yield, such as catalyst design, process temperature, thermal safety, substrate concentration, solvent systems, etc.

There are few articles[150,225] on the production of LA from C5 compounds such as xylose (Fig. 8; Table 8). However, some articles on the production of LEs from pentose route intermediates, as furfuryl alcohol, have been published in recent years.[135,173,175,188,229–232] The reason may be because LA and LEs cannot be solely produced by solvolysis from these C5 compounds. After hydrolysis of xylose to stable molecular furfural, it needs an additional hydrogenation step to furfural alcohol, which was previously regarded as a precursor for the target production of levulinate ester by alcoholysis reaction in alcohols. We have already discussed the negative effect of hydrogenation from a sustainability perspective. However, as the acid-catalyzed conversion of furfural alcohol to LA in aqueous solutions resulted in different intermediate or final products, side reactions such as polymerization and rearrangement can reduce the yield and selectivity of LA.[233–235]

As for glucose, some researchers have observed the high efficiency of metal chlorides, in particular $FeCl_3$, in the conversion of xylose biomass-derived to levulinic acid and its esters. Wang and co-workers reported a maximum LA yield of 68 mol% employing $FeCl_3$, together with NaCl, at 180 °C for 2 hours and lower yields by the catalytic action of $CuCl_2$, $AlCl_3$ and $CrCl_3$.[84] Zeolites were also tested as heterogeneous catalysts in the xylose dehydration to levulinic acid, obtaining a LA yield of 31 mol% at 170 °C for 3 hours.[236] Homogeneous catalysts, like sulfuric acid and methanesulfonic acid, allowed higher yields (up to 60 mol%) with both xylose and glucose-xylose mixture as substrates.[237]

To improve the yield of LA from xylose, a novel strategy employing biphasic systems was developed by using alkylphenol solvents as the organic layer for direct conversion of hemicellulose in three steps.[150] Hydrolysis of xylose in low concentration occurs in a biphasic aqueous-organic system; organic solvent 2-sec-butylphenol (SBP) was added for dehydrating xylose and extracting furfural from aqueous layer saturated with NaCl. Then by hydrogenation of furfural in the second step, furfural alcohol was slowly fed into another biphasic reactor, where conversion of furfural alcohol to LA occurs in an aqueous layer. It is worth noting that most of the furfural alcohol remains in SBP, which decreases its concentration in the aqueous layer and the rates of side reactions as well, with negative implications in terms of “Reducing Derivatives”. Adding NaCl into the system can significantly improve the partition coefficient of furfural from 50 % to 90 %, allowing a high yield of furfural in the organic phase 70 % yield of LA was obtained in this system at 25 °C.

Due to the high boiling point, 4-n-hexylphenol (NHP) and 4-propylguaiacol[207] were selectively used as solvents to remove LA to the organic phase and further distillation of LA from the top column. This strategy was proved to be efficient for converting xylose-hemicellulose-derived to LA with alkylphenol solvents in a biphasic reactor system, and should be further investigated in terms of “Inherent Safety”.

The organic solvent in specific biphasic organo-aqueous systems can play as an electrophile, transforming furfural into HMF by electrophilic substitution and avoiding the mandatory hydrogenation step in the pentoses route. Hu and co-workers have investigated the production of levulinic acid, methyl levulinate and ethyl levulinate through biphasic systems, dimethoxymethane DMM-water and DMM-alcohol, reporting levulinate yields up to 50 % using xylose as starting substrate.[139]

Table 7 Conversion of C-6 monosaccharides and disaccharide (Sucrose) to LA or LEs.

Feedstock	Catalyst		Conditions[a]	Time	Yield [b]	Cat. reuse[c]	Ref.
LA production							
Glucose	Mineral acids	H_2SO_4	140 °C	2 h	38 %	-	48
			170 °C	2 h	34 %	-	206
	Organic acid	TFA	180 °C	1 h	35 %	-	208
	Mineral acid	$CrCl_3$,HCl	140 °C	6 h	46 %	-	211
	Zeolite	$CrCl_3$, HY	145.2 °C	2.45 h	55.2 %	-	212
		Cr/HZSM-5	180 °C	3 h	64.4 %	50 % - 4 runs	213
	Graphene oxide	$GO-SO_3H$	200 °C	2 h	74 %	60 % - 5 runs	238
	Ion exchange resins	Amberlyst-36TM	140 °C	3 h	52.3 %	-	214
		Sn-Beta,Amberlyst-15	140 °C	12 h	45 %	-	215
	Heteropoly acid	ChH_4PWTi,	130 °C	8 h	76.1 %	73 % - 12 runs	218
Fructose	Organic acid	TFA	180 °C	1 h	45 %	-	208
		PTSA	88 °C	8.33 h	16 %	-	207
	Mineral acid	HCl	140 °C Water/Methanol	1.33 h	72 %	-	209
		NaCl, HCl	88 °C	8.33 h	34 %	-	207
	Ion exchange resins	Amberlyst XN	100 °C	9 h	16 %	-	239
	Zeolite	LZY	140 °C	15 h	43.2 %	-	240
LA esters production							
Glucose	Aluminium sulfate	$Al_2(SO_4)_3$	160 °C	2.5 h	64 % (ML)	~64 % - 5 runs	221
	Sulfated metal oxides	SO_4^{2-}/TiO_2	200 °C	2 h	33.2 % (ML)	20 % - 7 runs	210
	Montmorillonites	SO_4^{2-}/MMT	200 °C	4 h	48 % (ML)	-	241
		Al^{3+}/MMT	220 °C	6 h	60 % (ML)	~60 % - 5 runs	222
	Zeolite	Sn-Al-β	160 °C	5 h	43 % (ML)	39 % - 5 runs	242
		USY	180 °C	3 h	45 % (EL)	~35 % - 6 runs	219
		H-USY, SnO_2	180 °C	3 h	81 % (EL)	-	223
	Ionic liquids	NEt_3B-SO_3H	140 °C	24 h	6 % (EL)	-	243
	Nanoparticles	Nano-TiO_2	175 °C	9 h	61 % (ML)	-	220
	Heteropoly acid	$H_2Zr_1PW_{12}O_{40}$, Sn- β	180 °C	3 h	55 % (EL)	-	244
Fructose	Mineral acid	H_2SO_4	120 °C	30 h	56 % (EL)	-	245
	Ionic liquids	NEt_3B-SO_3H	140 °C	24 h	72 % (EL)	~72 % - 3 runs	243
	Zeolite	H-USY	160 °C	20 h	51 % (ML)	45 % - 5 runs	246
			160 °C	20 h	40 % (EL)	~40 % - 5 runs	246

Table 7 (continued)

Fructose	Sulfonic acid func. SBA-15	SO_3H–SBA-15	140 °C	24 h	57 % (EL)	57 % - 3 runs	129
	Supported phosphotung. acid	HPW/H-ZSM-5	160 °C	2 h	43.1 % (EL)	25 % - 4 runs	247
	Modified metal	K-HPW-1	150 °C Ethanol/Toluene	2 h	64.6 % (EL)	50 % - 5 runs	248
	Aluminium sulfated	$Al_2(SO_4)_3$	160 °C	2.5 h	49 % (ML)	-	221
	Sulfated metal oxides	SO_4^{2-}/MMT	200 °C	4 h	65 % (ML)	-	241
		SO_4^{2-}/TiO_2	200 °C	2 h	59 % (ML)	20 % - 7 runs	210
		SO_4^{2-}/TiO_2-ZrO_2	200 °C	1 h	71 % (ML)	30 % - 5 runs	249
		SO_4^{2-}/TiO_2-La_2O_3	160 °C	3 h	95 % (ML)	86 % - 5 runs	228
	Grafted carbon nanotubes	CNT-PSSA	120 °C	24 h	69 % (ML)	-	227
			120 °C	24 h	84 % (EL)	69 % - 5 runs	227
			120 °C	24 h	86 % (PL)	-	227
			120 °C	24 h	87 % (BL)	-	227
	Ion exchange resins	Amberlyst-15	120 °C	24 h	73 % (EL)	-	227
			120 °C	24 h	89 % (BL)	-	227
		Dowex 50Wx2	120 °C	8 h	73.4 % (BL)	51 % - 3 runs	127
	Silicotung. based	SnSiW-423	150 °C	2 h	70 % (EL)	~70 % - 7 runs	250
		SnSiW-423	150 °C	2 h	66 % (BL)	-	250
	Phosphotung. acid based	3-FPYPW	120 °C	10 h	82.5 % (ML)	73 % - 4 runs	251
	Nanoparticles	Nano-TiO_2	175 °C	1 h	80 % (ML)	40 % - 5 runs	220
	Carbon cryogel	UCC-S-Fe-300	200 °C	6 h	55 % (EL)	-	252
Sucrose	Sulfonic acid func. SBA-15	SO_3H–SBA-15	140 °C	24 h	27 % (EL)	-	129
	Modified metal	K-HPW-1	150 °C Ethanol/Toluene	2 h	35.4 % (EL)	-	248
	Supported phosphotung. acid	HPW/H-ZSM-5	160 °C	2 h	27.3 % (EL)	-	247
	Sulfated metal oxides	SO_4^{2-}/TiO_2	200 °C	2 h	43 % (ML)	-	210
		SO_4^{2-}/TiO_2-ZrO_2	200 °C	1 h	54 % (ML)	-	249
	Modified carbon	AC-Fe-SO_3H	200 °C	3 h	29 % (EL)	-	253
	Tungsten disulfide	WS_2	160 °C Microwaves	0.5 h	23 % (EL)	-	254
	Acid-sulfonated carbon	Zn-SC	100 °C Ultrasonic system THF/Ethanol	1 h	72.1 % (EL)	66 % - 7 runs	255
		Zn-SC	100 °C Reflux system THF/Ethanol	12 h	64.2 % (EL)	-	255

[a] using water as solvent, unless otherwise specified.[b] Methyl (ML), ethyl (EL), propyl (PL), butyl (BL) levulinate.[c] yield after N reuse cycles tested.

Table 8 Conversion of C5 monosaccharides to LA and LEs

Feedstock		Catalyst	Conditions[a]	Time	Yield[b]	Catalyst reuse[c]	Ref.
Xylose	Mineral acid	H_2SO_4	200 °C	0.13 h	64.4 % (LA)	-	237
	Organic acid	Methanesulfonic acid (MSA)	180 °C	0.25 h	64.7 % (LA)	-	237
	Metal salts	$FeCl_3$/ $FeCl_3$+NaCl	180 °C	2 h	48.5/68 % (LA)	52.5 % - 4 runs	235
		$CuCl_2{\cdot}2H_2O$	180 °C	2 h	34 % (LA)	-	235
		$CrCl_3{\cdot}6H_2O$	180 °C	2 h	25 % (LA)	-	235
		$AlCl_3{\cdot}6H_2O$	180 °C	2 h	26 % (LA)	-	235
	Zeolite	AZY0.25	170 °C	3 h	30.4 % (LA)	-	236
	Ion exchange resins	Amberlyst 70	150 °C	6 h	41.6 % (ML)	-	139
			160 °C	2 h	21.8 % (EL)	-	139
	Mesoporous zirconium silicate	KITZ20	200 °C	5 h	87.7 % (BL)	79.8 % - 4 runs	256
	Dual catalyst	Zr(20)-MCM-41 +$H_3O_{40}PW_{12}$	-	-	53 % (BL)	50 % - 4 runs	257
Xylose +Glucose	Mineral acid	H_2SO_4	200 °C	0.13 h	61.6 % (LA)	-	237
	Organic acid	Methanesulfonic acid (MSA)	180 °C	0.25 h	54.8 % (LA)	-	237
	Ion exchange resins	Amberlyst 70	160 °C	2 h	40.7 % (ML)	-	139
	Zeolite	Modified- Hβ	160 °C 1,3,5-trioxane	18 h	50.4 % (ML)	~50 % - 5 runs	258

[a]using water or alcohols as solvent, unless otherwise specified.[b] Methyl (ML), ethyl (EL), butyl (BL) levulinate.[c] yield after N reuse cycles tested.

3.4 Direct production from cellulose, hemicellulose and biomass (LCB)

Compared to the use of pure monomeric sugars, as fructose, glucose and xylose, and other precursors, the employment of raw complex lignocellulosic substrates in the production of levulinic acid and alkyl levulinates can provide a cheap and promising alternative for the industrial-scale production sustainability, reducing the disposal of potentially usable waste and increasing the development of agribusinesses and rural sectors, even though to date monosaccharides processing offers the highest product yields.[176] Besides the raw lignocellulosic feedstocks, many researchers have investigated the production of levulinates via hydrolysis of single-cell wall components of plants: cellulose and hemicellulose. Both abundant in nature, they lead to the production of value-added chemicals through hydrolysis to simple sugars and the subsequent acid catalysis of the latter; in particular for cellulose, the synthesis of levulinic acid and its esters passes through the production of the intermediate 5-HMF, being mainly rich in glucose, while for hemicellulose through the pentose pathway and thus by the route of furfural.[259] On the other hand, the use of raw lignocellulosic matrix, often of variable composition and unknown sugar content, determines the production of sugar mixture (both hexoses and pentoses) and consequently the increased complexity of the process. To economize the production, low cost raw lignocellulosic sources should be selected as fast-growing grasses and trees: switchgrass, giant reed, miscanthus, poplar; but also low-value municipal and industrial wastes: wheat straw, sugarcane bagasse, rice husk, corn stover, sawdust, pulp sludge, olive tree pruning, fruit peels.[44,176,259] The complexity and heterogeneity of these substrates require pre-treatment steps to improve subsequence yields and reaction rates.

Given the high efficiency and the relatively low cost, mineral acids have been intensely used and still employed in the industrial-scale production of levulinic acid and esters from LCB (Table 9). The most commonly used mineral acid catalysts are H_2SO_4 and HCl. The reactivity of the catalyst is highly related to the nature and concentration of the initial feedstocks; for example, HCl is particularly suitable for converting high calcium-containing biomass, as a paper mill and tobacco chops, because of the H_2SO_4 tendency to form precipitating $CaSO_4$, with possible reactor clogging effect.[260] Significant levulinic acid yields have resulted from the use of these acids in various lignocellulosic feedstocks: pretreated rice husks are employed by Bevilaqua et al.[261] at 170 °C for 1 h, resulting LA yields of 59.4 and 45.7 wt% for HCl and H_2SO_4 respectively;[261] paper sludge led to 31.4 wt% and 15.4 wt% of LA yield at 200 °C for 1 h under the action of diluted HCl and concentrated H_2SO_4 in Raspolli Galletti et al. studies;[260] wheat straw is another promising feedstock, analyzed by Chang et al.[262] who reported yields around 20 wt% at 200 °C for both catalysts;[262] liquefaction of bagasse and paddy straw have been tested with HCl at 220 °C by Yan et al.,[263] reporting LA yield of 22.8 and 23.7 wt%;[263] and fast-growing plants as giant reed that leads to producing LA yield of 24 wt% at 190 °C for 1 h.[264] On the other hand, the direct production from cellulose leads to higher yields, as 40.8 wt% at 150 °C for 6 h[265] or 43 wt% for 2 h.[266] The final LA concentration is strongly affected by the initial substrate concentration; a low feedstock concentration results in a higher yield of LA and esters because exceeding a particular biomass loading is conducive to the excessive occurrence of unwanted secondary reactions.[267] At the same time to ensure the industrial intensification of the process and avoid too high separation costs due to the low concentration products, the concept of high-gravity should be applied; i.e., a process operating at the highest possible concentrations of raw material.[203,268]

Given the difficult recovery of LA from the reacting mixture, a higher LA concentration is favorable since it leads to a lower energy-demanding purification and a reduced amount of wastewater, but this cannot be achieved by increasing the substrate loading infinitely. Thus, smart solutions have to be applied to optimize production.[176,203] A possible solution is the use of a biphasic system (water-organic system) in which the presence of the organic solvent helps stabilize the intermediates formed, decreasing the unwanted reactions and improving the product selectivity. Furthermore, selecting a solvent immiscible in water with a higher LA partition coefficient than water allows efficient LA extraction.[269] All polar aprotic solvents, as tetrahydrofuran (THF), gamma-valerolactone (GVL), dimethyl sulfoxide (DMSO), can stabilize the reactive intermediates and, for those miscible in water, it is possible to increase the immiscibility by adding salts to the aqueous phase. Cellulose deconstruction in a biphasic system (water-gamma-valerolactone) has been reported by Wettstein et al.,[270] performed in GVL and an aqueous solution of HCl and NaCl. The majority of LA was extracted by GVL at 155 °C, obtaining a yield of 51.6 wt% after 1.5 h.[270] The effect of GVL as solvent has also been analyzed in the conversion of hemicellulose in the presence of sulfuric acid by Mellmer et al.;[271] in this work, they highlighted how this polar aprotic solvent increased product selectivities and reaction rates, thanks to the stabilizing effect on the acidic proton relative to the protonated transition states. In particular, the solvent affected the activation energies of reaction steps, as dehydration of xylose to furfural.[271] Benefits on the reaction time and the occurrence of unwanted reactions have been shown by the substitution of traditional heating with microwave heating (MW); positive MW effects were confirmed in the conversion to LA of paper sludge, poplar sawdust, olive tree pruning[260] and cellulose[272] as raw starting substrates. The same or even higher yield was observed applying MW technologies but observing an evidence reaction time reduction: increasing LA yield from 21.3 to 26.4 wt% and decreasing time from 1 h to 15 min in the presence of HCl for conversion of poplar sawdust; LA yield from 18.6 to 20.1 wt% using olive tree pruning as substrate and reduction of reaction time by 45 min.[260] The improved production and rapidity of the system are due to side-wall effects decreasing and higher homogeneous heat distribution by microwave heating, which results in being more selective for polar substances changing their selectivities, and avoiding their thermal decompositions.[44,203,273]

Mineral acids have been successfully used even in the direct production of levulinate esters from cellulose and raw lignocellulosic biomass. Methanolysis of raw biorenewable materials, as bamboo and corn starch, has been reported by Feng et al.[274] Liquified bamboo was treated in a batch system in the presence of sulfuric acid in subcritical methanol, reporting a methyl levulinate (ML) yield of 27.7 wt% at 200 °C for 1 h. The group has tested various other substrates: corn starch resulting in ML yield of 48.7 wt% at 180 °C and microcrystalline cellulose with ML yield of 23.9 wt% at 200 °C, both after 2 h.[274] Wood, bagasse, and wheat straw were employed in the direct production of methyl levulinate and also waste sources as paper sludge; this last substrate has determined an overall ML yield of 27.7 wt% under mineral acid condition at 220 °C.[275] Using low concentration of sulfuric acid (≤ 0.02 mol/L), cellulose (concentration range 30-100 g/L) have reported ML molar yields around 50 mol%, near 200 °C and up to 2 h, according to different research groups.[276,277] Sulfuric acid was found to be very active also in the degradation of cellulose and more complex biomass matrix with ethanol, giving ethyl levulinate molar yields up to 60 mol%.[278] Several one-pot conversions to EL of different substrates have been reported in the literature: wheat straw was remarked by Chang et al.,[279] as a promising, cheap, widely available raw substrate rich in cellulose, efficiently converted into ethyl levulinate under the action of sulfuric acid in ethanol medium, resulting in an optimum yield of 17.9 wt%;[279] paper pulp, wood chips and switch grass have produced comparable results in term of EL, yield of 25.9, 16.6, 13.8 wt%, respectively.[280] The optimization of the acid-alcoholysis process has been investigated by Dai et al.,[278] thanks to the combination of sulfuric acid with an Al-salt ($Al(OTf)_3$); being a Lewis acid catalyst, the salt catalyst can better catalyze than sulfuric acid, which is a Brønsted acid, the isomerisation of glucose to fructose leading to higher EL yields. Comparing the production from cellulose in the absence and in the presence of the salt, obtained EL yield was 20.2 versus 53.7 mol%; and considering different substrates, the mixed-acid system determined yield of 64.7 mol% employing paper pulp, 54.3 mol% with pine wood and 53.7 mol% using bamboo as starting feedstock.[278] Changing the alcohol medium, mineral acids lead to the production of higher molecular levulinates as butyl levulinate; cellulose was tested in the presence of sulfuric acid in 1-butanol medium, obtaining a yield of 50 mol% in an autoclave at 200 °C for 30 min[281] or a yield exceeding 60 mol% operating with higher acid concentration.[282] Yield up to 40 mol% was obtained by using raw biomass, as Eucalyptus nitens wood[283] and rice straw.[284] Démolis et al.[281] also investigated the influence of different butanol isomers, highlighting that the primary alcohol group is more efficient, giving higher levulinates yields.[281]

Table 9 Production of LA and LEs from LCB via homogeneous catalysis.

Catalyst	Substrate	Conditions[a]	Time	Yield[b]	Catalyst reuse[c]	Ref.
Mineral acids						
HCl	Pretreated rice husks	170 °C	1 h	59.4 % (LA)	-	261
	Paper sludge	200 °C	1 h	31.4 % (LA)	-	260
	Wheat straw	200 °C	1 h	20 % (LA)	-	262
	Bagasse	220 °C	0.75 h	22.8 % (LA)	-	263
	Paddy straw	220 °C	0.75 h	23.7 % (LA)	-	263
	Giant reed	190 °C	1 h	24 % (LA)	-	264
	Poplar sawdust	200 °C	1 h	21.3 % (LA)	-	260
	Poplar sawdust	200 °C MW	0.25 h	26.4 % (LA)	-	260
	Olive tree pruning	200 °C	1 h	18.6 % (LA)	-	260
	Olive tree pruning	200 °C MW	0.25 h	20.1 % (LA)	-	260
	Cellulose	155 °C GVL/Water	1.5 h	51.6 % (LA)	-	270
H_2SO_4	Pretreated rice husks	170 °C	1 h	45.7 % (LA)	-	261
	Paper sludge	200 °C	1 h	15.4 % (LA)	-	260
	Wheat straw	200 °C	1 h	20 % (LA)	-	262
	Cellulose	150 °C	2 h	43 % (LA)	-	266
	Cellulose	150 °C	6 h	40.8 % (LA)	-	265
	Liquified bamboo	200 °C	1 h	27.7 % (ML)	-	274
	Corn starch	180 °C	2 h	48.7 % (ML)	-	274
	Cellulose	200 °C	2 h	23.9 % (ML)	-	274
	Wheat straw	183 °C	0.6 h	17.9 % (EL)	-	279
	Paper pulp	190 °C	1.7 h	25.9 % (EL)	-	280
	Wood chips	190 °C	1.7 h	16.6 % (EL)	-	280
	Switch grass	190 °C	1.7 h	13.8 % (EL)	-	280
	Bamboo	180 °C	3 h	53.7 % (EL)	-	278
	Cellulose	200 °C	0.5 h	50 % (BL)	-	281
H_2SO_4 + $CrCl_3$	Potato peel	180 °C	0.25 h	49 % (LA)	42 % - 3 runs	285
H_3PO_4	Cigarette butts	200 °C	6 h	49.6 % (LA)	-	286
Ionic Liquids						
$[BSMim]H_2SO_4$	Cellulose	160 °C	0.5 h	39.4 % (LA)	~ 39 % - 4 runs	287
[Bmim]Cl	Wood residues	220 °C	1.25 h	38.7 % (ML)	36.6 % - 5 runs	288
$[BSMim]H_2SO_4$	Mesocarp fiber	130 °C	1.4 h	14.7 % (EL)	-	33
$[C_4H_8SO_3Hmim]HSO_4$	Cellulose	180 °C	0.75 h	31.1 % (BL)	~ 31 % - 6 runs	289

[a]using water or alcohols as solvent, unless otherwise specified.[b] Methyl (ML), ethyl (EL), butyl (BL) levulinate.[c] yield after N reuse cycles tested.

Industrial scale production of LA and LEs is currently available on the market but not in sufficient quantities. Some of the reasons for the limited commercial-scale production of levulinic acid are production low yields, anti-corrosion equipment and materials cost, energy demand, and post-treatments cost. Difficulties in recovering LA at high concentration are due to the inherent physical properties of levulinic acid, which make this compound difficult to isolate. In addition, the low selectivity of homogeneous acid catalysts (mineral acids) leads to multiple undesirable products.[290] Developed by Fitzpatrick and patented by the Biofine Corporation[291], the Biofine technology eliminated some of the drawbacks in LA production, becoming one of the most known and industrially deployed technologies for the industrial production of LA from lignocellulosic biomass. Based on the acid-solvolysis by homogeneous mineral acids, the process involves a two-stages acid-catalysed reaction process. In a first plug flow reactor biomass feedstock is dehydrated to HMF between 200-230 °C, 20-25 bar, for less than 30 seconds and using mineral acids (1-4 %). Subsequently, LA production occurs by hydrolysis of HMF at 190-220 °C, 10-15 bar, for 15-30 min in a second continuous stirred reactor[292] (Fig. 9). The second reactor operates in the condition that allows to kept formic acid and furfural in the vapour phase, leading to a more simple separation of these products from LA. With yields between 59-83 % of the theoretical value, this semi-commercial technology can produce LA from 0.42 to 0.595 kg per kilo of cellulose.[50,293] The process co-produces also other valuable commodities including furfural, formic acid and lignin char.[285] The process defined conditions to suppress the formation of by-products and achieve high yields strongly. It employs reduced reactor volumes, minimised corrosion resistant materials, reducing the high equipment costs, but post-treatment neutralization steps for the catalyst are still necessary. Besides the Biofine process, the WALEVA project's technology proposes to convert waste LCB residues, as rice straw,[294] into levulinic acid. Exploiting 2.4 million tonnes of rice residues (referred to rice production in Europe in 2012) that would normally be incinerated, the Waleva process is able to reduce the CO_2 resulting from the disposal of this waste by 80 %, producing LA with a total yield of between 16-18 %, and a final product of 90-95 % purity.[295] For the production of levulinate esters as ethyl levulinate, Dibanet project aims to design a sustainable cost-effective process for the production of ethyl levulinate from lignocellulosic biomass, by combining the hydrolysis of monosaccharides to LA, then esterified to ethyl levulinate via mineral acids, with pyrolysis of the degradation biomass residues.[296,297] Among its various objectives, the project seeks to replace mineral acids with more environmentally and economically sustainable catalysts in terms of purification and recycling; solid acid heteropolyacids (HPAs) have been tested, obtaining yields of 76 % for ethyl levulinate with up to 4 times recycling.[298] At present, the use of mineral acids is still privileged in several industrial production plants or pilot plants (GFBiochemicals,[299,300] Segetis (acquired by GFBiochemicals in 2016),[301,302] Biofine[291]),[303] although research is moving towards the design of competitive heterogeneous catalysts or different homogeneous catalysts. These same advantages of mineral acids in downstream steps, i.e. purification and recycling, are not present in other homogeneous catalysts. The ionic liquids (ILs) gained great attention thanks to their stability, low vapor pressure, and easy separation and recyclability. Being easily tuned by varying ionic components, ionic liquids are versatile in cellulose and biomass transformation. SO_3H-functionalized ionic liquids have been tested in the production of LA from cellulose, obtaining its yield of 39.4 wt% at 160 °C for 30 min[230] and in the production of EL from oil palm empty fruit bunch and mesocarp fiber with yields of 13.1 wt% and 14.7 wt%, respectively.[33] Particularly active in the direct esterification of biomass-derived LA, ionic liquids, as 1-Methyl imidazolium hydrogen sulphate [MIM][HSO_4], catalysed the LA esterification to BL, obtaining a final yield of 89.6 mol% at 90 °C in 90 min.[92] In addition to the efficient catalytic activity, with the possibility to be recycled without loss of functionality (demonstrated 10 cycles for [Hmim][(HSO_4)(H_2SO_4)$_2$]),[304] ionic liquids have been tested as a solvent in alkyl levulinate production from biomass. Liang et al.[288] reported the important role of 1-butyl-3-methyl imidazolium chloride (BmimCl) in the depolymerization of cellulose, derived from wood residue, which produced a ML yield of 38.7 mol% in the optimum conditions.[288] Nevertheless, ionic liquid also present several drawbacks: not completely

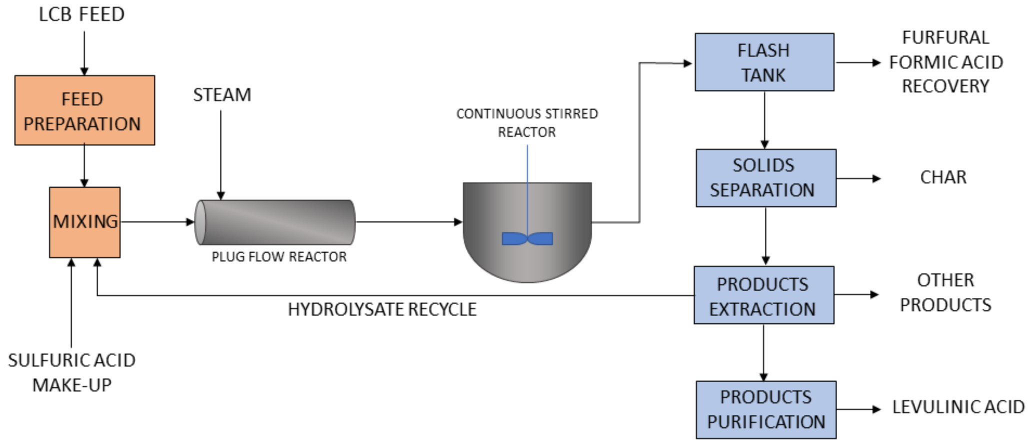

Fig. 9 Process scheme of the Biofine technology.[292]

environmentally friendly;[305] high viscosity, which reduces mass transfer in the liquid and requires the presence of water to improve it;[44,306] possible equipment corrosion, especially in fact of water; their low vapor pressure makes their recovery by distillation not suited; and last but not least, their high cost which undermines their use on an industrial scale (up to 100 times higher cost than organic solvents).[44,176,307]

Although homogeneous catalysts resulted strongly in biomass valorization, the industrial introduction of heterogeneous catalysis is one of the greatest challenges that industry faces moving towards a bio-based market and solving technological disadvantages, such as equipment corrosion, environmental pollution, and difficult recycling, typical of homogeneous acid catalysts. However, the development of heterogeneous catalysts is imperative from a practical and environmental industrial perspective. Most of the new synthesized and characterized catalysts are restricted to academic investigations, due to factors limiting their catalytic action (Table 10).[44]

The limited catalytic yield is mainly due to the difficult solid-solid interaction between catalyst and substrate and the catalyst deactivation. Mass transport is troubled by the difficult access to the active catalytic species into the solid or swelled biomass and further prevented by the deposition of solid by-products, such as humins and lignin-derived residues, leading to catalyst deactivation.[176,259] To increase productivity, solid acid-catalysts are developed and properly tuned, considering that an appropriate acid strength is crucial for converting cellulose and biomass to levulinates, especially in the reaction rate of H-bonded cellulose structure opening. Several studies demonstrated benefits by tuning the catalysts in the presence of two types of acid sites: Lewis and Brønsted acid sites. Although Brønsted acids generally carry out the hydrolysis of cellulose and hemicellulose and the subsequent conversion of fructose, xylose and other monomers, the presence of Lewis acid sites is also crucial for isomerisation reactions, such as glucose-cellulose-derived to fructose. Peng et al.[267] investigated the conversion of cellulose to levulinic acid, catalyzed by different metal chlorides, since metal salts show high catalytic activity and both types of acidity. Among those, $CrCl_3$ resulted quite effectively with LA yield of 67 % in 3 h.[267] $CrCl_3$ was also tested with H_2SO_4 to produce levulinic acid from potato peel waste, reporting a LA yield of 49 % at 180 °C for 15 min.[285] Particularly effective also aluminium phosphate ($Al_2(SO_4)_3$), it allowed high alkyl levulinate production: ML yield of 52 wt% at 200 °C for 6 h starting from softwood bark as substrate,[308] EL production yield of 36.4 wt% using cassava for 6 h at 200 °C.[309] Among the commercially available heterogeneous acidic catalysts reported for levulinic acid and esters production are zeolites, sulphated metal oxides, metal oxides, solid superacid[310] and ion-exchange resins.[308]

Zeolites have been deeply investigated in the acid-hydrolysis of sugar monomers but potentially employed also in the conversion of cellulose and raw biomass. The hierarchical Mordenite zeolites (H-MOR) has been synthesized and tested by Velaga and co-workers, obtaining promising results in the production of levulinic acid: yield of 56 % for 3 h using cellulose, and improved yield of 61 % using bamboo sawdust as starting substrate.[311] Furthermore, HY zeolite has been selected, thanks to its high catalytic reactivity as Brönsted acid, and with the addition of $CrCl_3$ (Lewis acid site properties), to obtain a hybrid catalyst and to catalyze the levulinic acid production from empty fruit bunch and kenaf with a yield of 29.2 and 22.7 wt%, respectively.[212] Bi-functionalized with zirconia, zirconia-zeolite hybrid (ZrY6) showed high efficiency in methyl levulinate production, leading to ML molar yields of 53 % from starch and 27 % from cellulose at 180 °C.[157] Zirconia and other metals are also very effective in the form of oxide, leading to the hydrolysis of cellulose and subsequence production of levulinic acid or esters with promising results: LA yield of 53.9 mol% from cellulose at 180 °C for 3 h catalyzed by zirconium dioxide;[312] sulfated metal oxides (especially SO_4^{2-}/TiO_2) produced a LA yield around 30 mol% starting from starch and lower yield, 10 mol%, using cellulose.[210] The acid solvolysis of lignocellulosic biomass can also be catalyzed by ion-exchange resins, such as Dowex and Amberlyst; these insoluble polymers can exchange specific ions in the reaction mixture to convert the initial substrates. Alonso et al.[313] reported converting cellulose to levulinic acid on Amberlyst 70, obtaining a high yield of 69 %;[313] while Amberlyst 36 was tested in the production from sugar beet molasses, obtaining 78 mol% of LA yield.[214] Due to stericity issues in the interaction catalyst particles and biomass and the consequent low yield, few studies are present on their use in biomass conversion to levulinic esters.

In contrast, they have been extensively tested in the production reaction from simple monosaccharides, precursors and esterification of levulinic acid.[127] Heterogeneous catalysts can provide an efficient and sustainable route in the synthesis of levulinic acid and its esters, replacing the problematic homogeneous acid catalysts. Furthermore, the possibility of precisely tuning and functionalizing them improves the process versatility and efficiency, especially in cascade biomass processes.

Although numerous functionalized heterogeneous catalysts have been already developed, as magnetic catalysts to facilizing the downstream separation steps, or multifunctional catalysts with ample amount of active sites, further advances are still necessary in view of greener biorefineries, keeping into account the "PYSSVR" concept: production cost; yield; stability; selectivity; versatility and reusability.[314]

Recent studies on the conversion of raw biomass as starting substrates to value-added chemicals have evidenced the promising use of macroalgae, as the third generation of biomass; some advantages of this class than lignocellulosic biomass are related to the absence of lignin in the structure and to the rapid growth rate associated to the high consumption of CO_2.[259]

Kang and co-workers tested the potentiality of Gelidium amansii (macroalgae) in the production of levulinic acid catalyzed by mineral acid, obtaining a yield of 43 %,[315] and Yamaguchi et al.[316] got a ML yield of 37 % from algae residues.[316]

Table 10 Production of LA and ELs from LCB via heterogeneous catalysis.

Catalyst		Substrate	Conditions[a]	Time	Yield[b]	Catalyst reuse[c]	Ref.
Metal sulfated	$Al_2(SO_4)_3$	Softwood bark	200 °C	6 h	62 % (ML)	10 % - 3 runs	308
		Cassava	200 °C Ethanol/Water	6 h	47.05 % (EL)	5 % - 2 runs	309
		Bagasse	180 °C	0.6 h	65.1 % (ML)	-	317
		Poplar powder	180 °C	0.6 h	62.7 % (ML)	-	317
		Bamboo powder	180 °C	0.7 h	64.2 % (ML)	-	317
		Cellulose	180 °C	0.7 h	70.6 % (ML)	65.3 % - 5 runs	317
			180 °C	0.9 h	70.1 % (EL)	-	317
			180 °C	1.25 h	53.7 % (iPL)	-	317
			180 °C	1.25 h	63.1 % (BL)	-	317
	$Fe_2(SO_4)_3$	Cellulose	220 °C	3 h	30.5 % (BL)	-	318
Zeolite	H-MOR	Cellulose	180 °C	2.5 h	56 % (LA)	-	311
		Bamboo sawdust	180 °C	4 h	61 % (LA)	-	311
	HY+ $CrCl_3$	Empty fruit bunch	145.2 °C	2 h	29.2 % (LA)	-	212
		Kenaf	145.2 °C	2 h	22.7 % (LA)	-	212
	ZrY6	Cellulose	180 °C Microwaves	3 h	27 % (ML)	-	319
		Starch	180 °C	3 h	53 % (ML)	-	319
	Micro-meso acidic H-USY	Wheat straw	200 °C	12 h	24.5 % (EL)	-	320
Metal oxide	ZrO_2	Cellulose	180 °C	3 h	53.9 % (LA)	~ 53 % - 3 runs	312
Sulphonic acid functionalised	SBA-SO_3H	Cotton straw	180 °C	6 h	18 % (LA)	-	321
	KCC-1/Al–SO_3H	Cellulose	200 °C	6 h	28.8 % (EL)	15.1 % - 5 runs	322
Mixed acid catalyst	Sn/ZrP-SO_3H, $Al(OTf)_3$	Kitchen waste	163 °C	7.6 h	52 % (EL)	-	323
	$Al(acac)_3$, PTSA	Cellulose	180 °C	5 h	72 % (ML)	61 % - 5 runs	324
	$In(OTf)_3$, PTSA	Cellulose	180 °C	5 h	70 % (ML)	-	325
	$In(OTf)_3$, Benzenesulfonic acid	Eucalyptus	200 °C	5 h	67 % (ML)	-	326
Ion-exchange resin	Amberlyst 70	Cellulose	160 °C GVL/Water	16 h	69 % (LA)	28 % - 4 runs	313
	Amberlyst 36	Beet molasses	140 °C	3 h	78 % (LA)	18 % - 5 runs	214
Ionic liquid	$[C_4H_8SO_3Hmim]HSO_4$	Cellulose	180 °C	0.75 h	31.1 % (BL)	28.9 % - 6 runs	289

[a] using water or alcohols as solvent, unless otherwise specified. [b] Methyl (ML), ethyl (EL) levulinate. [c] yield after N reuse cycles tested.

4. Separation and Purification Processes

In oil refineries, separation and purification steps are based on distillation technologies, together with liquid extraction, crystallization, absorption, adsorption, and use of membranes, accounting for 40-50 % of the total costs.[327] However, similar to a classical refinery, the biorefinery has to consider several factors that increase the complexity and the energy demand of downstream processes compared to oil refineries; such as low feed concentration, heterogeneity of the feedstock, inhibition issues, low product yields, and the high content of water and oxygenated compounds which might lead to complex mixture and azeotropes. These drawbacks affect the economy of scale and the total costs in which separation accounts for 60-80 %.[328,329] In particular, the presence of high functionalized lignocellulosic-derived groups, as hydroxyls, aldehydes, ketones, carboxylic, makes biorefinery's streams susceptible to thermal instability and therefore not favorably separable at high temperature.[329] The separation process is also aggravated by the high dilution of product streams, a direct consequence of reduced feed concentration to avoid the formation of degradation products such as humins.[28,330,331]

The presence of humins, along with the presence of mineral acid catalysts, is one of the major challenges in LA downstream processing.[28] On one hand, LA can form a wide range of derivatives that can make its recovery even more difficult. On the other hand, currently investigated methods to improve LA recovery are based on its reactivity and include the esterification to LEs, which can be considered, in this sense, easier to handle.

The recovery and purification of LA is strongly dependent on the type of lignocellulosic substrate and the technology used for its production. Unlike other biomass-derived platform molecules that can be produced via bioprocessing, LA can only be produced by acid-catalyzed chemical processes. Clearly enough, the use of homogeneous or heterogeneous acid catalysis already affects LA purification method. Typical biomass hydrolysis produces a diluted stream of LA (3-8 wt%), formic acid (1-5 wt%) and furfural (1-5 wt%) in water. Although levulinic acid does not form any azeotrope, water-furfural mixture gives a minimum-boiling heterogeneous azeotrope at 97 °C and a furfural content of 64.5 wt% and formic-acid-water mixture a maximum-boiling homogeneous azeotrope at 106.8 °C. This results in downstream processing, typically based on conventional separation schemes, mainly expensive and hostile to industrial scale-up.[332,333] Several patented[300,334–337] and experimental technologies have been developed to purify LA via gravimetric separation or liquid-liquid extraction combined with advanced distillation technologies.[332,333,338] For dilute high boilers as levulinic acid, liquid-liquid extraction results to be a potential efficient technique for fractioning the mixture. Traditionally based on the use of high molecular weight aliphatic amines and organophosphorus, liquid-liquid extraction has the main advantage to high recovery boiling and thermosensitive components, avoiding or minimizing the need to distill enormous amounts of solvent, usually water, which is highly energy demanding.[329] Recently, different solvents, such as ketones, alcohols, esters, ethers, and hydrocarbons, have been tested showing a high selectivity for LA over sulfuric acid in homogeneous acid-hydrolysis. Brouwer and his group[338] first designed a recovery process based on a furfural extraction section and then an acid fractioning of the mixture LA-FA. Non-polar solvents, as toluene and methyl isobutyl ketone (MIBK), showed high potential in removing furfural, while the extraction of LA and FA from the acid aqueous acid solution was by polar solvents as 4-tert-butylbenzenediol (TB) and 1-octanol.[338] Instead, energy and environmental comparison between MIBK and 2-Methyltetrahydrofuran (2Me-THF) as extractants of LA has been by Isoni and his group in order to define a techno-economic analysis and sustainability of biorefinery processes. Since the extracting organic solvent is recovered by distillation, MIBK leads to twice the amount of energy required for heating to boiling point, having a higher specific heat capacity (2.14 kJ/(kg K) versus 1.96 kJ/(kg K) of 2-MeTHF) and higher normal boiling point (118 °C versus 80.3 °C).[339] 2-MeTHF was identified as the best choice for energy cost, gases emissions and environmental sustainability, since it can be produced by biomass. Besides to alkyl levulinate, 2Me-THF is another potential fuel additive LA-derived and a promising solvent in biomass processing, thanks to its high stability in acidic conditions and low miscibility with water that leads to creating organic-aqueous biphasic system, extracting LA and other organic from the aqueous phase.[340]

The production of LA using ionic liquids (molten salts at ambient temperature), seems to be promising in terms of separation,[33,341] even though some research evidenced their tendency to co-extract sulfuric acid, making them less suited for LA extraction in sulfuric acid medium.[338]

A summary of the technologies investigated in the literature is proposed in Table 1, where a technical comparison is offered.[28] Sustainability issues related to downstream processes are discussed in the following section.

Being acid-free and highly volatile, alkyl levulinate are easily separable from alcoholysis products derived from carbohydrates and lignocellulose via distillation.[342] Li and co-workers reported separating products from methanolysis of cellulose by distillation technique that combines an atmospheric and vacuum distillation.[276] The downstream scheme leads to a product stream in which methyl levulinate was the major component of lower heavy fraction with purity over 96 mol%. N-dodecane was added to the mixture to help distill the heavy products as a desorption driving agent, and it has been detected in a small percentage in the final stream, together with levulinic acid.[276] Instead a new process for the preparation and purification of butyl levulinate (BL) from cellulose has been developed by Liang and his group; the purification scheme combines an extraction operation where the final BL is recycled and used to partially extract LA (its residue is further esterified to BL) with distillation steps. A final BL purity of 98 wt% is obtained after distilling the unreacted alcohol and washed with saturated sodium carbonate and water to neutralize the sulfuric acid and salts.[343] Distillation processes are also employed to separate and purify ethyl levulinate; in particular, several groups reported introducing techniques that combine reaction and separation steps in a single unit, as reactive distillation (RD). The advantages of RD are related to the continuous removal of products, pulling the chemical equilibrium towards the products, and particularly suitable for reactions hindered by the chemical equilibrium limitations, as esterification of LA to EL and other esters.[329,344] Vazquez-Castillo and his group designed a reactive distillation process which couples an RD column with two separation columns and leads to EL with a purity of 99.5 mol%; additionally, applying thermal coupling to RD, energy and cost reductions are in the range of 24-63 % and 8-43 %, respectively.[344] In literature, some works reported using pervaporation catalytic membrane reactor system (PVCMR) in which reaction and separation occur simultaneously, based on the permselective evaporation through the membrane. Unlu and coworkers obtained EL almost pure using a catalytic composite membrane in a PVCMR system.[107] The presence of humins, in soluble and/or insoluble form, increases the complexity of separation processes; extraction and/or membrane filtration allow to remove the humins in the products mixture. The use of toluene and other non-polar solvents has been tested with high extraction rates as an agent of selective extraction of EL without humins.[342] Being one of the most significant responsible for the total costs, choosing a specific separation technology has to be done in favorable conditions. Industrially, distillation is a good option in the following cases:[329]

- Boiling temperature in distillation (atmospheric or vacuum condition) has to be firmly lower than thermal degradation temperature for all components.
- The temperature difference between the boiling point of products to separate might exceed 5 °C.
- The product concentration in the distillate stream should be higher by 10 wt% than in the feed stream.

Separation technologies based on the affinity between components, as liquid-liquid extraction, absorption and adsorption are economically suitable in case of:

- Product and medium have to present differences in chemical affinity to obtain an efficient separation.
- The extractant owns a moderate level of bonding, strong enough to allow efficient extraction but not too strong to ensure successful regeneration.
- Low product concentration is only economically viable if it presents a high affinity for the extracting component.
- Minimising interactions with impurities in the reaction medium.
- Advantageous extractant/sorbent regeneration processes.

Finally, permeation processes are strongly dependent on the right material available. They can be applied in conditions:

- The product and medium have to show a difference in diffusivity, i.e. with the permeable material.
- Choice of a permeable, available, cost-effective material, which shows versatility with the feed variability.

Table 11 LA separation and purification processes (Adapted from [28]).

Downstream process	Pros	Cons	Impact on Green Chemistry Principles[16]	
			Positive	Negative
Vacuum distillation	Well-established technology	Energy demanding Undesired by-products formation	-	"Design for Energy Efficiency" "Reduce Derivatives" "Inherently Safer Chemistry for Accident Prevention"
Liquid-Liquid Extraction	Well-established technology	Large volume of solvent is required: sustainability disadvantageous	"Design for Energy Efficiency"	"Reduce Derivatives" "Less Hazardous Chemical Syntheses"
Reactive Liquid-Liquid Extraction	No additional processing required	Complicated	"Design for Energy Efficiency" ""Reduce Derivatives"	Depending on chemicals
Stripping with steam	High purity is obtained	Energy demanding	"Inherently Safer Chemistry for Accident Prevention"	"Design for Energy Efficiency"
Membrane separation	Minimizes undesired by-products formation	Costly Fouling problems	"Reduce Derivatives"	"Design for Energy Efficiency"
Adsorption	Simple and well-established technology	Low efficiency at industrial scale	"Inherently Safer Chemistry for Accident Prevention"	"Design for Energy Efficiency"
Ionic liquids	No additional process required	Costly Under development	"Prevention " "Reduce Derivatives"	"Design for Energy Efficiency"

5. Considerations on economic and environmental sustainability

To date, several technological issues have limited the economical manufacture of platform chemicals such as LA and LEs, e.g., the cost of raw material and equipment, the low yield of LA due to undesirable side reactions, difficulties in efficient product recovery, catalyst recovery costs, low energy inefficiency of the processes.[28]

Exploring some of these aspects, a necessary first consideration is related to the starting biomass or precursor. The required pre-treatments typically account for a substantial fraction of the total energy requirements and up to 20 % of the capital and operating costs,[2] thus being an obstacle to commercialization. Low cost, low input cultivation and highly available lignocellulosic biomasses, such as agricultural and forest residues and energy crops, should be preferred, also for laboratory scale-up.[203] The choice of the starting substrate has to be done considering the biomass supply chains and its economic analysis, which includes collection, processing and transport of the biomass but also the plant locations and social criteria like workers, investors and government.[203] Isoni et al.[339] have realized a techno-economic investigation of the levulinic acid production in Southeast Asia comparing two different scenarios, accounting location factors, such as biorefinery next to biomass source or biomass shipped to the biorefinery, and also sustainability factors like deforestation (impact on the CO_2-emissions) and soil depletion.[339] Selected the substrate, the specific pre-treatment is crucial for the optimization of the process; the research is advancing in this sense, for example substituting pre-treatments water-based to with others that use more favorable media: cheap, non-toxic, biodegradable, recyclable, and preferably derived from renewable resources in order to be economically and environmentally appealing. Examples under investigation are organic solvents, ionic liquids, and deep eutectic solvents.[2] Deep eutectic solvents have been identified not only for pre-treatments, favoring the delignification and solubilization of cellulose, but also as solvent for the subsequent conversion to added-value chemicals, as alkyl levulinates.[203]

A second aspect is related to the inefficient product separation and recovery for LA production, as discussed in the previous section. On the one hand, distillation is typically used for this purpose, but because of the wide range of the boiling points of the products, it is neither efficient nor economical. On the other hand, solvent extraction is complicated as by-products have similar polarity with respect to the main product and the use of large amounts of solvent is necessary to achieve high recovery.[37] Reactive extraction and reactive distillation methods are widely investigated. Concerning LA, the production of LEs overcome such limitations being more easily separated.

A third aspect is related to waste disposal and corrosion, which is related to the use of mineral acid catalysts, requiring expensive construction materials for both reactor and acid recovery plants, increasing the capital investment and operating costs.[37,176] Recycling the acid solvent mixture would be beneficial to the disposal problem from both environmental and economic standpoints, despite additional operating costs. The introduction of heterogeneous catalysts could be the only alternative to carrying out a more efficient and environmentally friendly acid-catalyzed biomass process. Although currently scarcely used on an industrial scale, heterogeneous catalysis does not suffer from equipment corrosion, high volume of wastewater and expensive and challenging recovery and recycling.[269] Furthermore, considering high selectivity and efficient and simple regeneration, the development of cheap heterogeneous catalysts, deriving from low-cost precursors, may constitute the key element in the green intensification of biomass valorisation.[203,269]

Finally, to improve the economics of the process, attention to the lignin should be paid; this lignocellulosic component is far too often underestimated, considered more similar to waste than a resource component. In the hydrothermal treatments of biomass for the production of levulinic acid and its esters, lignin is generally regarded as the main waste stream, being a solid hydro-char residue. As well as being a possible immediate source of energy recovery, lignin represents an origin of a large amount of bio-based chemicals, rich source of hydroxylic and carboxylic functional groups, potentially employable as substituents in polyurethane foam formulation, as adsorbents, precursors of catalysts, soil additives and energy store materials.[345,346] Due to the heterogeneous structure, its recovery can be a critical industrial challenge but several integrated biorefineries[347] have been designed, including it and significantly improving the overall process economy.[203] Depending on the primary target product asset, the lignin recovery could be designed as an upstream step, potentially advantageous thanks to the availability of organic solvent from pretreatments and efficient in the lignin fraction, or as a downstream step in the process.[203,347] Besides solvent-based fractioning, membranes could also be effectively used in lignin recovery.[347] From the perspective of integrated processes, humins are also a potentially valuable “waste” product. Produced by the degradation of sugars, furan and 5-HMF in the production of levulinic acid and alkyl esters, humins is a polymeric network of furanic derivatives containing sugar-derived moieties, that can be transformed into a range of valuable chemicals and fuels, through steam reforming for H_2 and other fractioning techniques.[348,349] Currently, lignin and humins are not recovered in the production process of LA and LEs, but, in line with the principles of biorefinery,[350] an integrated multiproduct biorefinery should be developed to improve sustainability and cost-effectiveness of the processes.[2,37]

From the environmental point of view, in literature, there are only a few but meaningful studies related to LA, ELs, and related biochemicals and biofuels. In 2015, Khoo and co-workers proposed an LCA for the Synthesis of 2-methyl tetrahydrofuran from various lignocellulosic feedstocks using an acidic pre-treatment, the Biofine process followed by the hydrogenation of LA.[351] The main results were that the energy used for the pretreatment was negligible with respect to that required for the separation of LA from furfural, and the authors highlighted that bio-based chemicals may not automatically be synonymous with "green". Therefore efforts should be made to ensure sustainability in particular for what concerns land-use footprint. Again in 2019, Khoo et al.[352] assessed the sustainability of various supply chains for the production of LA from different feedstocks with a more sophisticated LCA approach, aimed at a geographical comparison of LA production, concluding that the highest environmental impacts are caused by land use, fuel and agro-chemicals consumption.[352]

In 2015, Mukherjee et al.[353] discussed the sustainable production of HMF and LA by qualitatively comparing different substrates and reaction systems. The authors commended microwave irradiation-heated systems in their review because of their dual advantages of high product yields and low environmental footprint.[353]

Gonzalez-García et al.[354] (2016) analysed by means of LCA, four different scenarios characterised by the same raw material (wood chips) converted to soluble poly-saccharides versus LA to identify the most sustainable biorefining route. The results showed that the production had the worst environmental performances due to the acidic treatment, but this is no longer true if an economic revenue normalization is proposed. The study revealed many uncertainties and the authors concluded that further research should be done.[354]

In 2018, Leal Silva et al.[32] made a techno-economic and environmental assessment of the possible production routes for LA and ELs comparing different geographical locations, showing that the key factors affecting the performances are related to the inefficiencies in the reaction technologies and to the complexities in downstream processing (in particular with wastewater treatment, catalyst recycling). Attention is given to improve ionic liquids (that are currently too expensive to be used at industrial scale), reduce the formation of humins, avoid the use of organic solvents.[32]

In the same year, Isoni et al.[339] studied the sustainability of a biomass to LA biorefinery processes in Southeast Asia, showing again the issues related to land use and agricultural nutrients.[339]

In 2019, Hafyan and co-workers[278] studied the overall sustainability (i.e. simultaneously considering economic, environment, and safety aspects) for the production of LA from empty fruit bunch in Malaysia by means of acid-hydrolysis. Their main results confirmed what previously reported in literature: process utilities related to the separation of LA from water are the largest contributors to costs and environment, whereas acid hydrolysis is relatively safer than hydrogenation.[355,356]

Finally, in 2021, Kapanji et al.[357] proposed an LCA and sustainability assessments of biorefineries producing glucaric acid, sorbitol or levulinic acid annexed to a sugar mill. They showed that, despite the socio-economic attractiveness of the LA, it was the worst-case environmental scenario due to high loads from GVL production, associated with the manufacture, transportation and use of n-butyl acetate solvent and hydrogen from natural gas.[357]

In conclusions, there are several essential attempts in the literature to evaluate the sustainability related to LA and LEs, but a comprehensive and overall comparative quantitative study is still missing. Such study should be carried out to support aware decision making for the scale up and the industrial implementation of alternative production processes and technologies.

6. Conclusions

The energy transition is a significant structural change of the actual energy system, based mainly on unrenewable fossil fuels, towards a renewable energy system; key element in the policy of several countries around the world through the various agreements stipulated to achieve climate neutrality. In this panorama, biomass can significantly contribute to the achievement of targets, allowing the development of greener and more sustainable production processes of chemical building blocks and biofuels. Levulinic acid and alkyl levulinates are promising value-added platform chemicals, directly manufacturable from different biomass generations, particularly from lignocellulosic biomass (second generation).

This review has explored the different possible substrates, from sugar monomers to raw lignocellulosic biomasses and intermediate precursors, that produce levulinates mainly for catalyzed acid-solvolysis, and, in addition to the reaction phase, the different phases that characterize the production process: pre-treatment and product purification phase. Some significant outlooks are listed below based on what was discussed through this review:

1. Pre-treatment is a mandatory step in transforming LCB to levulinic acid and its esters to open its structure, containing crystalline cellulose and recalcitrant lignin. Several studies relate the employ of pre-treatment techniques to increasing product yields and emphasize the need to choose a method appropriate to the type of biomass. Diluted acid pre-treatments result to be the most common methods, especially with LCB, being highly efficient, albeit with some drawbacks: equipment corrosion, neutralization post-treatments and eco-toxicity. Considering all the different types of techniques and biomass affinity, combined pre-treatments can provide an efficient action, low energy demand, low corrosivity and pollution.

2. According to the recent literature, acid mineral homogeneous catalysts (H_2SO_4, HCl) are still widely used in converting raw biomass and sugars monomers to levulinic acid and alkyl levulinates thanks to higher product yields, low catalyst costs and high availability. Although advantageous from the reaction point of view, such catalysts are intensive cost-energy demanding as they require the use of specific corrosion-resistant materials and post-reaction neutralization treatments. Replacing homogeneous acid catalysts with green and efficient heterogeneous catalysts can be a critical challenge for the hydrolysis process in the future. The possibility of fine-tuning catalytic properties makes heterogeneous catalysts particularly suitable for dealing with substrates of variable composition. Catalysts with a dual-acid nature, Lewis and Bronsted acids are particularly active in the solvolysis of LCB to levulinates. The catalytic activity is combined with easy recovery and regeneration of these catalysts and no corrosion effects. In addition, the use of special aprotic polar solvents, as GVL, makes

it possible to extend the life of the catalyst by avoiding the formation of insoluble by-products, such as humins, which can deposit on the catalyst and poison it and to stabilize reactive reaction intermediates by preventing their degradation.

3. Separation and purification of biorefinery products have to consider various factors which affect their complexity: low feed concentration and heterogeneity of the feedstock, inhibition effects, low product yields, presence of insoluble by-products, high content of water and oxygenated compounds, possible azeotropes. Thus, the recovery and purification of levulinic acid and its esters largely depend on the starting biomass and the production technology. Although distillation is commonly used in industrial separation, techniques as liquid-liquid extraction are particularly suitable for dilute high boilers and strongly active compounds as levulinic acid. For alkyl levulinates, the downstream processes are less complex being acid-free and highly volatile; thus, they are easily separated from the alcoholysis mixture via distillation. Less explored but promising methods combine reaction and separation steps in the same system; reactive distillation (RD) and pervaporation catalytic membrane reactor (PVCMR) lead to high-purity products with possible reduced energy-cost-demanding.

Based on the current situation, future researches in the production of levulinic acid and alkyl levulinates should be focused on the development of intensive and direct conversion strategies, based on the one-pot cascade approach, which is particularly advantageous in terms of process economy, process time, work and resources management, and waste generation.[206] The development of efficient, cheap heterogeneous catalysts, preferably obtained from low-cost substrates, can convert a significant composition range of raw biomasses; the development of integrated-multiproducts biorefinery systems allows profit from the conversion of waste biomass residues or secondary reaction products, such as lignin and humins. In addition, industrial scale-up must include a techno-economic analysis, which considers cost-contributing factors as logistics, i.e. pre-processing, transportation and storage, to have a clear and accurate evaluation of the project feasibility. With the aim of sustainable exploitation of renewable feedstocks to LA and its esters, quantitative comparative assessments, integrating economic, environmental and process safety aspects should be carried out to support a conscious decision making with respect to the scale-up and the industrial implementation of alternative production processes and technologies.

Conflicts of interest

"There are no conflicts to declare".

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