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Review

Novel Routes in Transformation of Lignocellulosic Biomass to Furan Platform Chemicals: From Pretreatment to Enzyme Catalysis

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Abstract: The constant depletion of fossil fuels along with the increasing need for novel materials, necessitate the development of alternative routes for polymer synthesis. Lignocellulosic biomass, the most abundant carbon source on the planet, can serve as a renewable starting material for the design of environmentally-friendly processes for the synthesis of polyesters, polyamides and other polymers with significant value. The present review provides an overview of the main processes that have been reported throughout the literature for the production of bio-based monomers from lignocellulose, focusing on physicochemical procedures and biocatalysis. An extensive description of all different stages for the production of furans is presented, starting from physicochemical pretreatment of biomass and biocatalytic decomposition to monomeric sugars, coupled with isomerization by enzymes prior to chemical dehydration by acid Lewis catalysts. A summary of all biotransformations of furans carried out by enzymes is also described, focusing on galactose, glyoxal and aryl-alcohol oxidases, monooxygenases and transaminases for the production of oxidized derivatives and amines. The increased interest in these products in polymer chemistry can lead to a redirection of biomass valorization from second generation biofuels to chemical synthesis, by creating novel pathways to produce bio-based polymers.

Keywords: furan-based chemicals; biocatalysis; lignocellulose; 5-hydroxymethylfurfural; furfural; pretreatment

1. Introduction

The increasing interest in renewable, bio-based polymers has resulted in the quest for new synthesis routes for the production of polymer building blocks. This interest is further reinforced by the general concern regarding sustainability demands and environmental issues of modern-day societies. Polylactic acid, polyhydroxyalkanoate and other biomass-derived thermoplastic polyester products have been widely used to replace the traditional petroleum-based polyester products, thus paving the way for the industrial production of bio-based chemicals [1]. However, the monomers of these bio-based polymers are mainly synthesized from refined sugars derived from first generation feedstocks, consequently increasing the need for exploitation of non-food renewable biomass-based monomers to support the sustainable development of polymer industry. Similar to the "food versus fuel" conflict, lignocellulosic biomass offers a potential solution towards the exploitation of sugars in sources that would otherwise be discarded, compared to first generation sugars deriving from the food industry.

Lignocellulosic biomass is the most abundant renewable carbon source on the planet with an estimated annual production of 2×10^{11} tons [2]. Lignocellulosic biomass is mainly comprised of forest and agricultural residues and has traditionally been valorized as a feedstock for the production of second-generation biofuels. According to the Department of Energy, in the USA alone there are produced 1.3 billion tons of dry lignocellulosic biomass per year, of which agricultural residues contribute 933 million tons per year, while 368 million tons per year originate from forest wastes [3]. However, a sharp increase in the number of publications in the field of furan-based monomers research over the last five years indicates a possible shift of the biorefinery concept from the production of fuels towards the production of value-added chemicals [4].

Due to its recalcitrant nature, lignocellulosic materials are difficult to handle, therefore, a standard process has been established, in order to render these materials more amenable to downstream treatments. This process typically involves an initial pretreatment step, which holds a key role in the fractionation and separation of the different fractions of lignocellulosic biomass, namely lignin, hemicellulose and cellulose. The following step includes the chemical or enzymatic hydrolysis of cellulose and hemicellulose with the aim to release the monomeric sugars of each fraction [5]. The monomeric sugars can then be utilized as carbon sources for fermentation processes for the production of biofuels, such as ethanol and methane [6,7], or a repertoire of different valuable compounds, such as lactic acid, succinic acid and omega-3 fatty acids [8–10]. In addition, biomass-derived monosaccharides can serve as starting materials in chemical or enzymatic conversion processes towards the synthesis of advanced chemicals and compounds with different applications, such as in polymer industry, in drug synthesis or as nutraceuticals [11]. Among these chemicals, the most interesting section of chemical synthesis includes the platform chemicals, which can in turn lead to bio-based monomers and plastics. This part has recently received increased attention as an alternative to traditional petrochemically synthesized polymers, aiming to produce furans, an otherwise undesired product for microbial fermentation, as a building block for further use [12].

Numerous reviews concerning furan-based monomers published in the last few years underline the growing importance of these renewable sources. Uniquely, the furan ring is characterized by interesting peculiarities including its pronounced dienic character that renders it susceptible to Diels–Alder reactions towards polymerizations with suitable dienophiles. Furans, such as the *2,5-furandicarboxylic acid (FDCA)*, are moreover considered appropriate renewable substitutes for the corresponding benzene-based monomers (i.e., terephthalic acid) [13]. According to the report of the U.S. Department of Energy, FDCA is listed among the top 12 value-added chemicals from biomass nowadays and is considered a highly promising platform chemical with numerous applications in many fields [14]. Its structural analogy to terephthalic acid renders it a suitable candidate as a building block for the synthesis of polymers, such as polyethylene furanoate (PEF), which has been heralded as a green alternative of the petroleum-derived poly(ethylene terephthalate) (PET). PET has an annual market size of approx. 50 million tons and the use of FDCA represents a promising approach to obtain biomass-derived polyester, and fully or partially replace oil-based materials [4]. The application of FDCA is, however, not restricted to PEF and other polyesters, as it can be also used for preparation of polyamines and polyurethanes [15]. Apart from FDCA, *2-furancarboxylic acid (FCA)* also possesses significant potential for use as a monomer in polyesters, as it can be dimerized via a condensation reaction with aldehydes and ketones, and the resulting dimers bear a structural similarity with the bisphenol series, thus introducing novel properties to polyesters [16].

The valorization process of lignocellulosic biomass towards the production of furans is accomplished by means of chemical catalysis, thus involving the use of expensive metal catalysts or solvents that are also detrimental for the environment [16–19]. For this reason, over the last few years there has been an attempt to shift the valorization process towards the use of biocatalysts, as they require mild, less costly conditions and are environmentally friendly. In that context, much attention has been paid to utilizing furans as substrates for the production of chemicals as building blocks for the production of monomers, including FDCA and FCA, aiming to demonstrate environmentally-friendly bio-based

polymer synthesis. However, the use of such high selectivity catalysts means a cascade of chemical reactions with numerous products, each presenting different benefits and possible pathways towards the end product [20]. In order to accomplish this, an arsenal of different enzymes including, among others, oxidases and peroxygenases, are required for the production of FDCA, while transaminases can also function as possible catalysts for the synthesis of amines. The aim of this review is to provide information on an overall process for the production of furans and furan-based derivatives from lignocellulosic biomass, by means of biocatalysis. The introduction of such a process could, therefore, function as a sustainable and eco-friendly approach towards the replacement of the traditionally petrochemically synthesized polymers.

2. Conversion of Lignocellulosic Feedstocks to Monomeric Sugars

Lignocellulosic biomass, as aforementioned, is the most abundant plant material on the planet and is mainly derived from perennial herbaceous plant species and woody crops, while other major sources are agricultural and forest residues [21]. However, the deconstruction process of the plant cell wall presents a bottleneck for the industrialization of lignocellulose biorefining, due to its recalcitrant nature. The term "*biomass recalcitrance*" refers to the rigid structure of the plant cell wall and the subsequent difficulties it poses to the enzymatic treatment of the lignocellulosic biomass [22]. In order to overcome the recalcitrant barriers of lignocellulosic biomass and to render these materials more vulnerable to subsequent chemical or enzymatic treatment, a procedure known as *pretreatment* is required. Pretreatment is the initial step of the biomass conversion process to monosaccharides, as depicted in Figure 1. Pretreatment aims to alter the rigid structure and chemical composition of the biomass feedstocks and, therefore, increase the digestibility of cellulose or hemicellulose, which are the main sources of utilizable sugars [2]. Another key role of pretreatment is to achieve efficient fractionation of three biomass constituents, namely lignin, cellulose and hemicellulose, thus yielding pure streams and facilitating the subsequent valorization processes [23]. However, the type of pretreatment can vary, depending on the need of each application. Therefore, the appropriate pretreatment can be designed taking into consideration whether a specific fraction of lignocellulose is of particular interest. Understanding how the chemical composition and physical structure of biomass contribute to its recalcitrance, as well as their effect on the enzymatic hydrolysis of lignocellulose, would greatly help to improve the current pretreatment technologies, and probably promote the development of novel pretreatment processes [22].

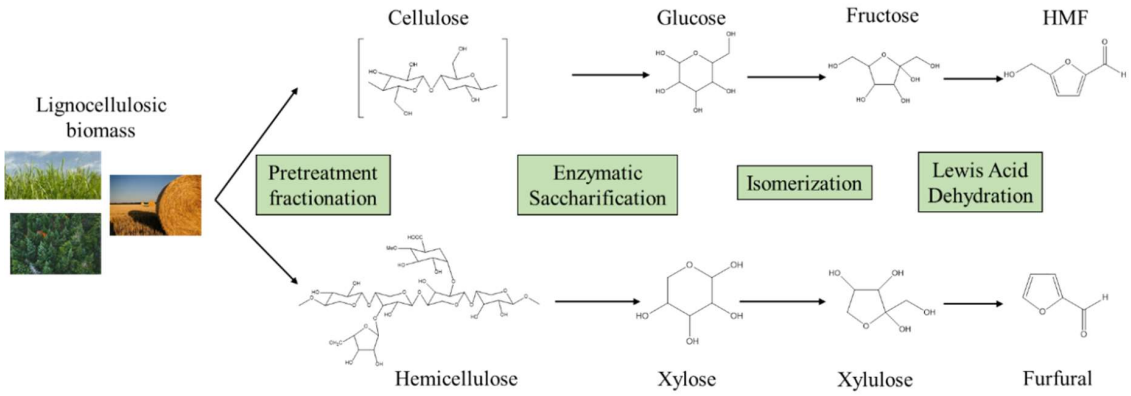

Figure 1. Overview of the process illustrating how furans can be produced from lignocellulosic biomass.

2.1. Plant Cell Wall Composition

Lignocellulose is composed of a complex structure of different compounds, in which cellulose, hemicellulose (polymeric carbohydrates) and lignin (an aromatic polymer) are intertwined together. The exact proportions of each fraction can vary depending on the type of the plant cell wall.

Lignocellulose also contains pectin, proteins, extractives and inorganic compounds in smaller amounts [24,25]. Different types of feedstock carry different amounts of each compound. Softwood, which is found at forest residues, consists of approximately 33–42% cellulose, 22–40% hemicellulose and 27–32% lignin [26]. The respective amounts in hardwood materials are 38–51% cellulose, 17–38% hemicellulose and 21–31% lignin [27]. Grasses contain 25–95% cellulose, 20–50% hemicellulose and 0–40% lignin [28,29]. The complex matrix constructed from the combination of these three fractions has a protective role for the plant against assault from the microbial or animal kingdoms, as it blocks the access of microorganisms or enzymes to the structural sugars of the cell wall and, therefore, their degradation. In terms of biomass valorization towards the production of furans, cellulose and hemicellulose fractions are those of main interest for the production of hexoses and pentoses, respectively. Hexoses can be subsequently utilized for the catalytic production of *5-hydroxymethylfurfural (HMF),* while pentoses represent the starting material for the production of *2-furaldehyde (furfural, FA),* as shown in Figure 1.

Cellulose is the largest and most abundant single component of lignocellulose with its percentage in the plant cell wall ranging between 35% and 50% depending on the type of the biomass. The cellulose fragment is composed of monomeric units of *D*-glucose linked together linearly with 1-4-*β* glucosidic bonds, thus enabling a stretched chain conformation with hydrogen bonds linking these chains into flat sheets. In addition, the packing of multiple cellulose strands leads to the creation of crystalline fibrils [30]. The crystalline nature of cellulose is partly responsible for the mechanical strength of plant tissues, as well as the difficulty in its disruption by enzymes. Cellulose exhibits a high degree of polymerization (higher than 10,000), which renders it less flexible and insoluble to water and most other solvents, even though this does not apply to glucose and its oligomers [26]. The enzymes responsible for the disruption of cellulose are cellulases and mainly involve four types of enzymes: endoglucanases, cellobiohydrolases, β-glucosidases and lytic polysaccharide monooxygenases, each providing a unique function for the conversion of cellulose to glucose. Cellulose has always been in the center of attention when it comes to second generation biofuels and especially bioethanol, since glucose produced from its disruption can function as a substrate for fermentative microorganisms for the production of ethanol. However, lately reports show that cellulose can be utilized also for other applications, such as the production of prebiotic cellooligosaccharides [31]. Production of HMF, not only from lignocellulosic biomass but also from other residual streams such as food wastes, is at the forefront in the synthesis of novel bio-based materials, as reviewed by Menegazzo et al. [32].

Hemicellulose is the second most abundant group of polysaccharides of lignocellulosic biomass. It is comprised mainly of pentose sugars, such as xylose and arabinose, exhibiting a degree of polymerization of 100 to 200, while hexose sugars, such as glucose, mannose and galactose are also present in small amounts [26]. The xylan backbone can be branched with its monomers decorated with acetyl and methyl groups or cinnamic, ferulic, glucuronic and galacturonic acids. These monomers, along with their decorations, can vary depending on the origin of each type of lignocellulose and function as the connections between lignin and hemicellulose [33]. There are indications that hemicellulose binds non-covalently to cellulose fibrils, thus resulting in a complex matrix that exhibits great resistance to enzymatic invasion and provides mechanical strength to the plant tissue. Due to its non-crystalline nature, hemicellulose is more susceptible to depolymerization than cellulose, an aspect of its behavior that is exploited by many deconstruction strategies, which include either a physico-chemical pretreatment, with the use of solvents and high temperature and pressure conditions or an enzymatic treatment upon addition of hemicellulose-degrading enzymes, or even both processes [26]. Indeed, many studies have demonstrated that hemicellulose removal leads to an increased yield of cellulose conversion [34,35]. Moreover, hemicellulose removal through efficient biomass fractionation further expands the potential of exploiting the pentose fraction for the production of, among others, furan-based valuable chemicals, such as FA, which has recently exhibited increased popularity, as reviewed by Luo et al. [36].

Lignin is the most abundant substance composed of aromatic moieties in nature [37] and it is composed of three basic monomeric units, namely *p*-hydroxyphenyl (H), guaicyl (G) and syringil (S)

units, in different ratios depending on the origin of the plant [26]. Lignin represents the compound that provides structural reinforcement and resilience to the plant tissue, protecting it against invasion from pathogens and insects [38]. In the plant cell wall, lignin is connected to hemicellulose, and the subsequent complex is intertwined around cellulose. Therefore, lignin restricts the access of hydrolytic enzymes to cellulose and hemicellulose as a physical impediment. However, aside from its physical restrictions, it has been proved that lignin irreversibly absorbs cellulases, thus preventing them from reaching cellulose [39–41]. Hence, the effective enzymatic treatment of any material demands a delignification step, which is mainly accomplished by the pretreatment. Lignin is only soluble in organic solvents and not in water, and for that reason the most effective pretreatments for lignin removal are organosolv or alkali-catalyzed organosolv processes [34,42]. However, enzymatic digestibility is not exclusively dependent on lignin removal. For example, dilute acid pretreatment removes only a part of lignin, but the enzymatic digestibility of cellulose can also be increased due to hemicellulose removal, lignin redistribution and other structural changes induced [22]. Within the frame of a furan-based valorization process of lignocellulose, lignin remains as a side stream that can be utilized for numerous potential applications [43].

2.2. Fractionation Technologies

Fractionation is a term used to describe the effective separation of each fraction of lignocellulosic biomass with the highest possible purity. As described above, this separation is achieved by pretreatment, which aims to alter or remove the structural and compositional impediments for hydrolysis and increase the yield of monomeric hexoses or pentoses from cellulose or hemicellulose, respectively [2]. For developing an effective pretreatment technology within the frame of furan-based valorization of biomass, efficient fractionation holds the key role in the overall process. Separation of biomass into a cellulose-rich lignin-free solid pulp, which will be subsequently hydrolyzed to glucose, and a hemicellulose-rich liquor containing lignin that can easily precipitated and removed, will allow for obtaining clean fractions for the production of furans. Other parameters to be considered are the reduction in the biomass particle size, the increase in cellulose accessibility, as well as the absence of inhibitory products that can cause adverse effects in a subsequent step. Inhibitory compounds include carboxylic acids, furan derivatives and phenolic compounds that are produced as sugar degradation products during pretreatment [44,45]. Although HMF and FA are not considered undesired products in an integrated biorefinery for the production of furans, they might both affect the performance of isomerases, cellulases and/or hemicellulases, and reduce the sugar yield [46], while other compounds, such as formic, acetic or levulinic acid might also affect the dehydration step towards the production of furans. The type of pretreatment can vary depending on either the origin of the feedstock or the downstream process and the fraction that is of particular interest. Various pretreatment processes target mainly at breaking the linkages between the different biomass components through high temperature, pressure conditions and/or the use of chemical catalysts. In general, there are many types of pretreatment that can be roughly summed up in four categories: physical, chemical, physico-chemical and biological pretreatment.

Physical pretreatment typically involves the mechanical treatment of the lignocellulosic biomass, the objective of which is to reduce the particle size and increase the surface accessibility of biomass to hydrolytic enzymes. Low particle size along with effective stirring techniques are of utmost importance for maximizing the subsequent hydrolysis yield [47]. The most prominent types of mechanical treatment include chipping, grinding and milling, depending on the desirable particle size. Extrusion is also another promising process that subjects biomass to heating, mixing and shearing, which leads to physical and chemical modifications of lignocellulose during the passage through the extruder [6,48]. However, the power requirements of such processes are relatively high, especially for low particle size demands, thus limiting their industrial use.

Chemical pretreatment catalyzed by different compounds, such as alkali, acid, organic solvents and ionic liquids, has been utilized as an effective method of lignocellulosic biomass fractionation. The use

of alkali is based on the ability to solubilize lignin and increase cellulose digestibility, while exhibiting low cellulose/hemicellulose solubilization [49]. Pretreatment with NaOH has been demonstrated to cause cellulose swelling and decrease its degree of polymerization and crystallinity, which further results in destabilization and dissolution of the lignin structure [50]. Another alkali showing great potential in lignocellulose pretreatment is $Ca(OH)_2$, also known as lime, which catalyzes lignin removal together with hemicellulose deacetylation and it can be easily recovered upon a post-treatment with CO_2 [51]. Alkali compounds are often used in low concentrations as bonus catalysts to physico-chemical pretreatments. On the contrary, the use of acid is based on the degradation and removal of hemicellulose fraction. Acid pretreatment can be performed by the use of either concentrated or diluted acid for the dissolution of hemicellulose. However, the implementation of concentrated acid encompasses equipment corrosion and acid recovery drawbacks, as well as high operational costs, making it unfavorable for commercial scale. On the other hand, the use of diluted acid not only solubilizes hemicellulose but can also hydrolyze it to its monomers, producing fermentable sugars. One of the drawbacks of acid pretreatments is the formation of furans, which are inhibitory substances for the growth of fermentative microorganisms and the production of ethanol [52]. However, these substances can be used efficiently for the increase in the overall yield of a furan-centered biorefinery concept. The most commonly used acid is H_2SO_4, while hydrochloric, phosphoric and nitric acid have also been used [53]. Finally, the use of fumaric and maleic acid as catalysts has been related to lesser amounts of FA produced compared to processes with H_2SO_4 [54].

Organosolv pretreatment employs the use of organic solvents, where the lignin fraction can be dissolved and, thus, removed in the liquid fraction. Upon solvent evaporation in the liquor, the water-insoluble lignin is precipitated and recovered in a relatively pure fraction [55]. Moreover, the use of organic solvent causes cellulose swelling and increases its degradability. Organosolv pretreatment is combined with other types of pretreatment for the efficient fractionation of biomass to its constituents. Organic solvents or their aqueous solutions that are commonly used involve methanol, ethanol, acetone, ethylene glycol and tetrahydrofurfuryl alcohol. By the use of a mixture of water and organic solvent, it is possible to collect both hemicellulose and lignin to each solvent, respectively, since hemicellulose is soluble in water and lignin is soluble in organic solvents. However, in organosolv procedures, effective removal of solvents through the appropriate separation techniques is required, as they may be inhibitory to enzymatic hydrolysis or sugar fermentation [56]. In addition, the increased cost for the industrial use of these solvents leads to the preference for easy to separate solvents with low molecular weights and low boiling points, such as methanol and ethanol. Organosolv is a very promising process within the frame of a furan-based biorefinery process, as it allows for obtaining lignin-free fractions, namely a cellulose-rich solid fraction and a hemicellulose-rich liquor that can be used for the production of HMF and FA, respectively.

Physicochemical pretreatment involves the simultaneous treatment of biomass with high temperature and pressure conditions upon the addition of chemicals as catalysts. This type of pretreatment combines the effect of chemical solvents on biomass structure, together with bond cleavage and fractionation through the harsh temperature and pressure conditions. The most widespread physicochemical pretreatment for lignocellulosic biomass is steam explosion. It is a hydrothermal process, where biomass is subjected to pressurized steam for several seconds or minutes followed by a sudden depressurization. The explosive decompression leads to a mechanical rupture of the plant cell wall polymers, thus enabling hemicellulose removal to the aqueous solvent and separation of the cellulose fibrils, rendering them more amenable to enzymatic hydrolysis. In addition, the harsh mechanical conditions affect the lignin fraction, leading to a temporary redistribution of its constituents [57]. During steam explosion pretreatment, the formation of acetic acid is very common due to the hemicellulose acetyl groups' exposure to high temperatures. This is the reason why many studies suggest the use of acid in low concentrations in order to increase the hemicellulose degradation. Further degradation of hemicellulose-derived sugars can lead to the formation of furans, such as FA, and HMF as well as formic and levulinic acid [51]. In general, steam explosion pretreatment represents a process that does

not require the use of hazardous materials. Another process for biomass pretreatment is liquid hot water pretreatment, where biomass is exposed to high temperatures (160–230 °C), although without the immediate decompression step. This process leads to the solubilization and removal of hemicellulose, while slightly affecting the structure of lignin and cellulose [39].

Another interesting physicochemical pretreatment is the Ammonia Fiber Explosion (AFEX). This process follows the principle of steam explosion pretreatment, as the material is incubated with liquid anhydrous ammonia in temperatures ranging from 60 °C to 100 °C with a subsequent release in pressure. This leads to the rapid expansion of the ammonia, yielding a solid pulp in which the cellulose fibers are swollen and less crystalline. While this process removes only a small part of the lignin and hemicellulose fraction, it has been shown to disrupt the lignin–carbohydrate linkages and increase the enzymatic digestibility of the material. This is probably attributed to the partial removal of lignin that adsorbs the cellulolytic enzymes, which are responsible for cellulose degradation [58]. Another advantage of this pretreatment process lies in the limited formation of by-products that can inhibit the downstream biological processes, mainly phenolic fragments of lignin, as well as the easy separation of ammonia in spite of its high volatility [59]. Finally, wet oxidation is a pretreatment that subjects lignocellulosic biomass to high temperatures (170–200 °C) and pressures (10–12 bar O_2) for 10 to 15 min, employing oxygen or air as an oxidative catalyst. This process has been demonstrated to achieve effective fractionation of biomass and solubilization of hemicellulose and lignin, depending on the solvent used, for the subsequent production of ethanol [47,60]. However, even though wet oxidation is able to remove lignin efficiently, the cost of oxygen and chemical catalysts can be significant impediments for the industrialization and the development of such technologies.

The *biological treatment* of lignocellulosic biomass involves the use of microorganisms, mainly for the degradation of lignin and hemicellulose, leaving the cellulosic structure almost untouched. The key microorganisms involved in biological pretreatment are the brown and white-rot fungi that produce several lignin-degrading enzymes, such as laccases and peroxidases for the efficient degradation of lignin [61]. Similar to all pretreatment processes reported above, biological pretreatment can be combined with other treatment types for the production of a cellulose-rich material susceptible to enzyme digestibility. As an example, Itoh et al. used a combination of biological and organosolv pretreatment for the effective production of ethanol [62]. However, while biological pretreatment offers advantages such as low capital cost, low energy demands and no use for chemicals, all in mild environmental conditions, its use is limited by low hydrolysis rates and time requirements [56].

Summarizing all the above, pretreatment is a process that aims to efficiently fractionate the polymeric constituents of the plant cell wall of lignocellulosic biomass. Fractionation can either occur upon the use of extreme mechanical, physical or chemical environments that cause disruption to the linkages among lignin, hemicellulose and cellulose, however with a toll. The effective separation and recovery of each fraction can lead to high capital costs or increased formation of by-products. In order for the pretreatment to be effective and cost-competitive, there is a need for the design of custom processes depending on both the specifications of the raw materials and the targeted end-products.

2.3. Enzymatic Hydrolysis of Cellulose and Hemicellulose

As described in Section 2.1, cellulose consists of *D*-glucose units linked together with β-glucosidic bonds. Its structure exhibits a high crystallinity index, therefore hampering its disruption. The breakdown of cellulose towards the production of glucose can be achieved either by the use of chemicals (though the use of acids or ionic liquids) or enzymatically by the use of cellulases [50]. While the chemical hydrolysis of lignocellulosic biomass has been the norm in the past, the enzymatic approach offers a more targeted, effective and environmentally friendly way to produce glucose. However, the complete deconstruction of cellulose in real feedstocks is a hard procedure that requires an arsenal of enzymes, each with its unique role. Hydrolytic cellulases are divided into three classes: exo-1,4-β-D-glucanases (cellobiohydrolases, CBHs, EC 3.2.1.176), endo-1,4-β-D-glucanases (EGs, EC 3.2.1.4) and β-glucosidases (BGLs, EC 3.2.1.21). Exo-1,4-β-D-glucanases attach to the ends of

the cellulose chains moving alongside the fiber releasing cellobiose units. Endo-1,4-β-D-glucanases hydrolyse internal glucosidic bonds randomly within the cellulose chain and, finally, β-glucosidases produce glucose either through the hydrolysis of cellobiose or through the cleavage of glucose units from cellooligosaccharides [63,64]. Lytic polysaccharide monooxygenases (LPMOs) are another class of enzymes with oxidative activity that have been shown to act synergistically with hydrolytic enzymes to boost the degradation of polysaccharidic substrates and increase the sugar yield [65]. Currently there is a great repertoire of commercially available cellulolytic cocktails for efficient biomass hydrolysis to monosaccharides, mostly produced by thermophilic filamentous fungi [66]. In addition, numerous monoenzymes have been cloned and expressed heterologously in eukaryotic hosts; this facilitates not only the study of mode of action of specific enzyme activities, but also the construction of tailor-made cocktails targeted for specific substrates [67–69]. Contrary to cellulose, hemicellulose is a heterogeneous polymer with a variety of substitutions that requires many enzymes for its deconstruction. Exo- and endo-xylanases cleave the xylan chain producing xylooligosaccharides, while β-xylosidases produce xylose from the cleaved xylooligosaccharides [70–73]. Mannanases and β-mannosidases function similarly in mannan. The side groups of hemicellulose can be removed by a variety of different enzymes, including α-galactosidases, α-L-arabinofuranosidases, α-glucoronidases, acetyl xylan esterases and feruloyl and p-coumaroyl acid esterases.

Inhibition of Enzymatic Hydrolysis

Cellulose deconstruction is a rigorous procedure that may be inhibited on many levels. The main factor inhibiting the enzymatic digestibility is the aforementioned complex structure of the plant cell wall. The matrix formed from the intertwined polymers of lignin and hemicellulose around cellulose, impedes the access of the cellulolytic enzymes to the cellulose fraction. Therefore, pretreatment is a key step for the overall yield of the process, as an effective fractionation will remove lignin and hemicellulose, the first and foremost obstacles. However, the cellulose hydrolysis holds itself as a process with many challenges.

Firstly, substrate composition is a key factor affecting the enzyme performance. It is known that many cellulases and hemicellulases attach themselves on the cellulose fibers through one of their domains, namely the carbohydrate-binding module (CBM) that promotes stabilization of the enzyme onto the carbohydrate substrate and coordinates the hydrolysis [74]. Non-productive adsorption of enzymes on lignin can occur, which can reduce the loading of active biocatalysts and, subsequently hamper the hydrolysis yields. Development of efficient pretreatment strategies that minimize the lignin content in cellulose and hemicellulose fractions is of pivotal importance in order to eliminate the adverse effects of residual lignin [23]. Substrate concentration also affects the overall saccharification rate, as operating at high solids conditions (above 12% wt.) can be detrimental due to the high viscosity of the mixture and the subsequent poor mass transfer conditions. In their work, Katsimpouras et al. portrayed the importance of the stirring technique to the yield of the hydrolysis, by comparing a traditional stirring system with flasks to an alternative free-fall mixer [47]. The sharp increase in cellulose conversion and glucose release that was observed in the free fall mixer under high initial solids content, confirms the advantages of effective mixing. These findings are very important for obtaining a high glucose syrup that is a prerequisite in order to produce a high-fructose syrup to be targeted for furans within the frame of a furan-based valorization process.

On another note, hydrolysis can be inhibited either by pretreatment degradation products (phenolic compounds, furans, carboxylic acids), as described above, or by the end-product of the process. During the enzymatic deconstruction of cellulose, released glucose shows a typical product inhibition to β-glucosidases [75], which leads to accumulation of cellobiose in the hydrolysate. Cellobiose, in turn, is also a strong inhibitor to cellobiohydrolases, impeding their function [76]. Therefore, in a typical hydrolysis process, reaching the full potential of glucose release is practically impossible, since the cellulolytic enzymes activity will be hampered due to accumulation of inhibitors. Hence, when fermentation is applied as a subsequent step of the process, in order to counteract against this

problem, simultaneous saccharification and fermentation strategy (SSF) is preferred, when possible. In this process, the fermentative microorganism is added to the hydrolysate containing the cellulases, fermenting the existing glucose, while it is simultaneously produced. This way, the cellulolytic enzymes are relieved from their inhibitors, continuing the cellulose deconstruction, while the fermentative organism keeps consuming the produced glucose, increasing both the cellulose conversion and the end-product formation. It is profound that the effective degradation of cellulose is a multi-factor process. Considering all the aforementioned factors, as well as the possibility of variations in the pH or temperature optima of the enzymes or the microorganisms and the production of other inhibitors, such as formic acid [77], it is evident that cellulose hydrolysis is a matter of extensive research on many fronts. Therefore, in order to reach high yields, taking into account and combining multiple factors is of pivotal importance.

2.4. Isomerisation of Hexoses and Pentoses for the Production of Furan Derivatives

Throughout the literature, many reports describe different chemical routes for the transformation of glucose to HMF [17,18], and of pentoses to FA [78], by using metal catalysts, ionic liquids and other methods. However, the high cost of such materials, combined with the necessity of post-purification, raised the need for the development of a cost-effective, environmentally friendly process for the conversion of glucose to HMF. The production of furan derivatives from lignocellulose-derived sugars under less severe reactions requires as a first step the isomerization of glucose and xylose to fructose and xylulose, respectively. These ketoses can dehydrated more easily than aldoses in the presence of Lewis acid catalysts towards the corresponding furans, namely HMF and FA [79,80]. In order to reach high yields of furans, the development of an effective isomerization step is of utmost importance.

The enzymatic isomerization of glucose to fructose requires the activity of *glucose isomerase*, one of the largest-volume commercial enzymes typically used for the production of high-fructose syrups from starches [81]. Production of fructose from corn liquor glucose has been demonstrated on an industrial scale by the commercially available immobilized enzyme preparation Sweetzyme IT (Novozymes) from *Streptomyces murinus*. [82]. However, the isomerization reaction is restricted by a thermodynamic equilibrium, at around 50%, preventing glucose from being converted in high yields. One way to shift this equilibrium towards fructose is the addition of sodium tetraborate in the reaction. This occurs because borate ions react with glucose and fructose, attaching themselves onto the second carbon of the ring, forming ionized esters. These complexes shift the equilibrium of the reaction as they are not recognized by the isomerase and, therefore, do not participate in the reaction. In general, borate ions show higher affinity to ketoses than aldoses in the equilibrium between borate and borate esters. That is why the reaction equilibrium is shifted towards the direction of fructose and not glucose [83,84]. As a result, the default 50% conversion of glucose can increase to as much as 80% [85]. This way, it is possible to produce HMF at high yields by means of a method with high selectivity that is also environmentally friendly. In a recent study by Wand et al., it was verified that the addition of borate to a ratio of 0.5 to sugar could significantly increase isomerization of glucose- and xylose-rich streams from pretreatment of corn stover, achieving approximately 80% glucose and 90% xylose conversion [85].

Furthermore, hemicellulose constitutes a large part of the plant cell wall aside from cellulose, whose main representative in most plants is xylan. In this perspective, the aforementioned system for the production of HMF by means of glucose isomerization, could be employed also for the valorization of xylose towards the production of FA. Similar to glucose, xylose can be converted to FA with the use of metal catalysts. However, by using an isomerase, xylose can be transformed to xylulose; dehydration of xylulose to FA is easier upon the use of acid or base catalysts [86,87]. This indicates the possibility for the development of a system where both glucose and xylose produced from the hydrolysis of lignocellulose can undergo an isomerization step and a subsequent dehydration step for the production of HMF and FA, all in a one-pot process (Figure 1). This way, the biorefinery process can be further integrated to encompass the valorization of xylose in addition to glucose, preventing the hemicellulose side stream from being discarded entirely.

3. Enzymatic Conversion of Furans to Building Blocks for Polymer Synthesis

Furans have been in the spotlight of biotechnological research as either inhibitors in processes such as microbial fermentation or, more recently, as starting materials in the chemical synthesis of different valuable monomers, as depicted in Figure 2. Throughout the years, many sources report the use of microorganisms to metabolize furans [88]. However, the mechanisms employed by microorganisms to metabolize furans are complex and the conversion is accomplished with a number of different enzymes secreted. In addition, working with microbial cultures presents other problems, such as optimum pH and temperature conditions of the organism, as well as the need of downstream processes for purification and recovery of the final product. For these reasons, there is a need to seek catalysts that can selectively transform furans in a controlled manner, be easily removed from the reaction medium and require mild conditions to function. As a result, during the last few years, much attention has been given to discovering enzymes that can catalyze the conversion of furans. The most common biotransformation reactions of furans include oxidation, reductive amination and reduction of furan aldehydes to alcohols. These modifications are discussed below and some future perspectives in the field of biocatalysis are described.

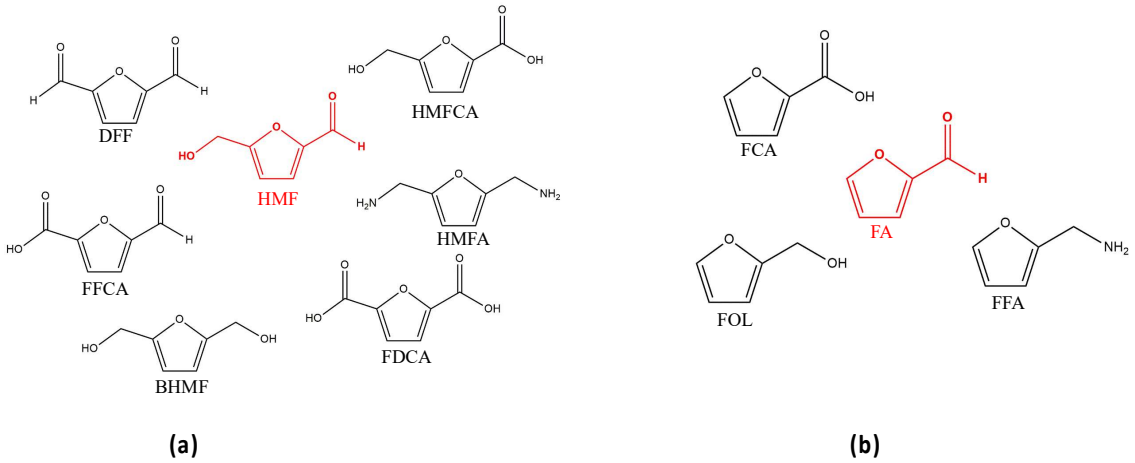

Figure 2. Overview of different monomers originating from (**a**) HMF and (**b**) FA. **HMF**: 5-hydroxymethylfurfural, **DFF**: furan-2,5-dicarbaldehyde, **HMFCA**: 5-hydroxymethyl-2-furancarboxylic acid, **FFCA**: 2,5-formylfurancarboxylic acid, **FDCA**: 2,5-furandicarboxylic acid, **HMFA**: 5-(hydroxymethyl)furfurylamine, **FA**: furfural, 2-furaldehyde, **BHMF**: 2,5-bis(hydroxymethyl)furan, **FCA**: 2-furancarboxylic acid or furoic acid, **FFA**: 2-furfurylamine, **FOL**: 2-(hydroxymethyl)furan.

3.1. Oxidation Routes of Furans

3.1.1. Oxidative Reactions of HMF

As mentioned above, the most interesting compound that can be derived from furans is FDCA, which is a substitute for the petrochemically synthesized terephthalic acid. FDCA can be produced from HMF by following two routes (Figure 3). In the first route, HMF is converted to *5-hydroxymethyl-2-furancarboxylic acid* (*HMFCA*), while in the second route HMF is converted to *furan-2,5-dicarbaldehyde (DFF)*. Both routes transform each respective chemical to *2,5-formylfurancarboxylic acid (FFCA)* which can, in turn, lead to FDCA. All steps in the above process and oxidation reactions require catalysts that can perform oxidation in alcohols and aldehydes. Due to the promiscuity in the mode of action of these oxidative enzymes, different activities have been reported to successfully participate in this cascade, as reviewed by [20]. The main enzyme activities implied include alcohol oxidases, galactose oxidases (GOs), 5-hydroxymethylfurfural oxidases, laccases, as well as catalases and peroxygenases.

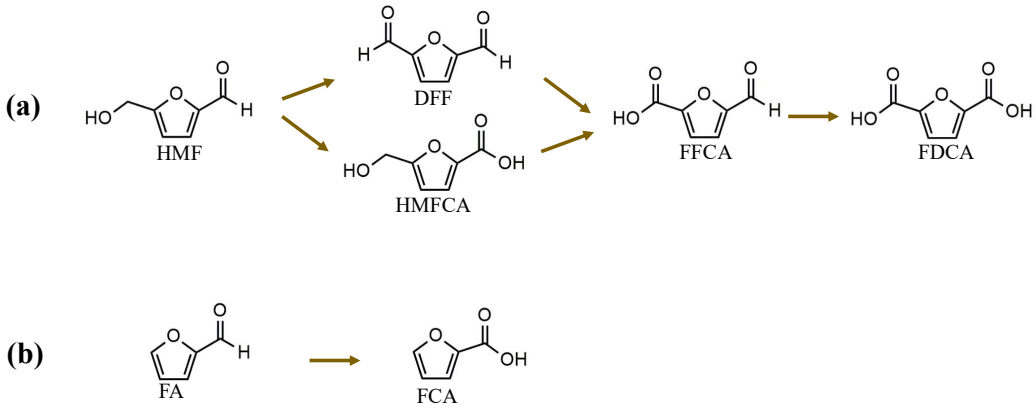

Figure 3. Schematic representation of oxidation of furan-derivatives that have been reported in the literature (**a**) HMF to FDCA, (**b**) FA to FCA. **HMF**: 5-hydroxymethylfurfural, **DFF**: furan-2,5-dicarbaldehyde, **HMFCA**: 5-hydroxymethyl-2-furancarboxylic acid, **FFCA**: 2,5- formylfurancarboxylic acid, **FDCA**: 2,5-furandicarboxylic acid, **FA**: furfural, 2-furaldehyde, **FCA**: 2-furancarboxylic acid or furoic acid.

In 2013, Krystof et al. [89] reported the use of a one-pot system of 2, 2, 6, 6-tetramethylpiperidine-1-oxyl (TEMPO) and lipase for the conversion of HMF to FDCA. This system includes a chemical catalyst (TEMPO) for the oxidation of HMF to DFF, combined with the activity of a lipase for the formation of peracid that catalyzes further oxidation to FDCA. In 2015, Carro et al. [90] tried to produce FDCA by means of a fully enzymatic cascade reaction. In that study, an aryl-alcohol oxidase (AOO) was employed, with the aim to perform all the oxidative steps required. However, while AAO successfully catalyzed the production of HMFCA in high yields, further oxidation was inhibited from the hydrogen peroxide produced in the reaction. For that reason, the authors performed the same reaction by adding an unidentified peroxygenase (UPO) as a subsequent step after the action of AAO, eventually producing FDCA in a yield of 91%. Serrano et al. [91] also investigated the effect of an AAO from *Pleurotus eryngii* on HMF for FDCA production. While AAO was demonstrated to efficiently oxidize HMF to HMFCA, further oxidation to FDCA was inhibited. However, by using HMFCA as an initial substrate to the AAO, the enzyme could successfully transform the substrate to FDCA. H_2O_2 produced during the reaction has an inhibitory effect on the second oxidation step, therefore a catalase was added, leading to complete transformation of HMF to FDCA after 12 days.

All the above indicate the ability of AAO enzymes belonging to the AA3 CAZy family (EC 1.1.3.7) to perform the oxidation of HMF. However, due to their limited ability to perform all three oxidation steps to FDCA, some report the oxidative ability of other enzymes of the AA3 family, such as glucose oxidases (EC 1.1.3.4), alcohol oxidases (EC 1.1.3.13) and pyranose oxidases (EC 1.1.3.10). Dijkman et al. characterized an HMF/FA oxidoreductase HmfH on a genetic level [92]. Following this, due to the fact that it was not possible to obtain the enzyme by means of expression [93], they sought for homolog enzymes that led to an HMF oxidase (HMFO) from *Methylovorus* sp., strain MP688. The HMFO again produced FFCA in high amounts, however the latter's low degree of hydration did not permit its further hydration to HMF. For that reason, by solving the crystal structure and introducing a double mutation, a 1000-fold increase in the catalytic efficiency of the enzyme on FFCA was achieved, finally producing FDCA in higher yields. Viña-Gonzalez et al. [94] tried to follow a similar mutational pattern on the amino sequence of an AAO in order to render it able to perform all three oxidation steps required for FDCA production. Indeed, while the wild type AAO initially strongly impeded the linkage of FFCA in the catalytic site of the enzyme, by introducing a tryptophan residue to a mutant carrying a H91N mutation that resembles the active site and structure of the HMFO, a 6-fold increase in the production of FDCA from HMF was achieved. Although the actual FDCA production yield was relatively low

(3%), that study reported for the first time an enzyme catalyzing complete HMF conversion to FDCA, paving the way for novel biocatalysts for furan valorization.

Enzymes of the Recently Revisited AA5 Family

The members of the broad AA5 family of CAZy database (http://www.cazy.org/AA5.html) have recently attracted significant interest regarding their potential in catalyzing oxidative modifications of furan derivatives. This group encompasses oxidases that require oxygen as a receptor (EC 1.1.3.-), including GOs (EC 1.1.3.9), glyoxal oxidases (GlOs) (EC 1.2.3.15), alcohol oxidases (EC 1.1.3.13) and raffinose oxidases (EC 1.1.3.-). Among other oxidative enzymes, GOs and GlOs have been reported to catalyze the conversion of furans, similar to AAOs and HMFO described above. Over the last years, there has been an increasing number of studies examining the potential of these enzymes in cascade processes on HMF conversion.

The first report of an AA5 enzyme acting on HMF was from the group of McKenna et al. [95], where the ability of a custom-developed variant of a GO from *Fusarium graminearum* to produce FDCA was examined. GO was able to convert HMF to DFF, but not to further oxidize it to FDCA. For that reason, an *Escherichia coli* periplasmic aldehyde oxidase (PaoABC) that was shown to be active on HMF, DFF and FFCA was employed to study whether the production of FDCA was possible. The key advantage of PaoABC in the process lied in the fact that it did not require the hydrate form of FFCA, contrary to other catalysts used in the process. Indeed, by adding both GO and PaoABC to HMF, production of FDCA was observed, although incomplete, due to the fact that PaoABC additionally produced HMFCA from HMF, which is a poor substrate for GO. Hence, in a subsequent experiment, GO was allowed to completely oxidize HMF to DFF prior to the addition of PaoABC to the system, thus accomplishing complete transformation to FDCA. Catalase was also added in the system to relieve the oxidative enzymes from the H_2O_2 produced throughout the process and provide the O_2 needed. A one-pot process was designed based on these findings [96]. A horseradish peroxidase (HRP) was added in the HMF-GO-PaoABC-catalase system and was found to significantly boost the activity of GO towards DFF production. This way, the HMFCA production was shifted, leading to 100% production yield of FDCA.

In 2015 Qin et al. examined the oxidation of HMF using an array of enzymes [97]. Firstly, a xanthine oxidase (XO) from *E. coli* producing HMFCA at a yield of 94% after 7 days, without progressing in further oxidation steps, was used. Secondly, three laccases were employed to boost the production of FFCA using TEMPO as a mediator. The highest conversion achieved was 82% yield, while lower yields of 4% and 10% were observed for DFF and FDCA, respectively. Finally, an enzyme cascade of GO, HRP and catalase to produce DFF from HMF was developed. The final step included the use of a lipase B (CAL-B) to convert DFF to FDCA with a yield of 88%.

Recently, Karich et al. attempted to design an enzyme cocktail to benefit from both routes of the FDCA synthesis process, including a UPO, a GO and an AAO [98]. In particular, it was supported that GO's and AAO's role was to oxidize the HMF towards HMFCA and DFF, respectively, and produce H_2O_2, while UPO's role was double; it was employed as oxidative factor to HMF and its oxidized derivatives, as well as relief agent of the H_2O_2 that was produced throughout the reaction. With this experiment, it was proved that the production of FFCA was rapid, while the FFCA to FDCA conversion was the most time-demanding step of the process. However, after 24 h, an 80% FDCA yield in the reaction was successful, while HMF was almost entirely converted to its oxidized derivatives.

Daou et al. studied the oxidation of HMF with three GlOs from the *Pycnoporus cinnabarus* [99]. Even though none of these enzymes exhibited HMF conversion yield over 40%, *Pci*GlO2 and *Pci*GlO3 activity was doubled upon the addition of catalase. The main oxidized product of HMF conversion was HMFCA. In order to bypass the inability to oxidize further HMFCA, an AAO was utilized in tandem with GlOs. Eventually, after AAO oxidized HMF to FFCA, GlO was added to the reaction in presence of catalase, producing small, but considerable, amounts of FDCA.

Mathieu et al. recently discovered a novel AAO from *Colletotrichum graminicola* that is able to efficiently catalyze the oxidation of aryl alcohols but demonstrates weak activity towards carbohydrates [100]. As such, AAO (EC 1.1.3.7) was reported as the first member of the AA5 family, whose activity is typically similar to the flavin-dependent glucose-methanol-choline (GMC) oxidoreductase family AA3. In the same work, it was demonstrated that AAO was able to oxidize HMF more efficiently than other biocatalysts previously reported; however, the enzyme could efficiently oxidize HMF towards DFF, but could only partially convert HMFCA in FFCA, with a yield of 54%.

While most enzymes require external co-factors to perform the oxidation reaction, such as (NADPH/NADP+)-dependent oxidases, this does not seem to be the case for enzymes belonging to AA5 family. The majority of members of this family represent copper-dependent enzymes which are easy to produce and purify, while they can function under no other requirement to perform the oxidation [101]. This is the reason why these enzymes can contribute significantly to the furan valorization procedure. However, in any case, it is evident that a cascade of enzymes is required in order to either reach the final steps of the sequential oxidations or achieve high yields in the final step. In most cases, the use of biocatalysts, such as catalases or peroxygenases, is required in order to alleviate the system from the adverse effects of the H_2O_2 produced, especially in case of the AA5 family members. Nevertheless, it is a promising observation that through protein engineering, mutants of a single enzyme can perform the entire oxidative pathway, even at low yields. As a result, further investigation can potentially transfer research from the current whole-cell to a single-enzyme strategy, thus significantly boosting the bioconversion process.

3.1.2. Oxidative Reactions for FA

Similar to HMF, FA also displays a potential for oxidative conversion, leading to the formation of *2-furancarboxylic acid (furoic acid, FCA)*. Early reports mention this process as a bio-detoxification process in fermentation, thus utilizing whole-cell catalysis for the reduction of FA [94,102,103]. However, further studies have been conducted in order to identify the specific enzymes involved in FA degradation.

A TEMPO-lipase system that was developed for HMF transformation was shown to effectively oxidize FA to FCA [89]. Kumar et al. tested the ability of 15 different Bayer-Villinger monoxygenases (BVMOs) to oxidize FA [104]. Among them, a phenylacetone monooxygenase (PAMO, EC 1.14.13.92) was shown to convert FA to FCA as the main product, achieving a 60% conversion yield after 12 h. However, a small amount of another by-product of oxidation reaction, which was identified as the formyl ester, was observed. This ester represents an intermediate compound that can be further transformed into the corresponding alcohol and formic acid [104]. The above results verify the possibility of effectively valorizing FA towards the production of its oxidized derivatives. Since FA can be formed by the hemicellulose-derived sugars, its valorization is a prerequisite towards lignocellulose biorefineries integration. For that reason, the promiscuity of utilizing oxidative enzymes on FA as a substrate can potentially contribute to achieve this goal.

3.2. Reductive Amination

Furfulylamines represent an interesting group of compounds that can be produced from the reductive amination of furans. They have numerous applications as starting materials in the synthesis of polyamine biopolymers and pharmaceuticals [105]. *2-Furfurylamine (FFA)*, a primary amine that can be produced from FA, is often used as a modifier in high performance thermosets due to its crosslinkable furan ring, where the introduction of furan groups can increase the crosslinking densities of the resulting polymer, and further enhance its thermal stability due to the formation of furfurylamine bridges during polymerization [106]. *5-(Hydroxymethyl)furfurylamine (HMFA)*, the amine occurring from reductive amination of HMF, has been patented as a curing agent in epoxy resins, besides its potential application in pharmaceutical industry as an intermediate compound in drug synthesis [107–109]. A high-titer synthesis of furfurylamine on an industrial scale is an attractive alternative to benzylamine and derivatives for the production of bio-based polymers with high-quality features, especially for

biomedical applications [110]. The current chemical process for the synthesis of furfurylamines occurs upon the addition of a hydrogenation catalyst under high pressure via multiple steps and leads to by-product formation and other issues related to the sensitivity of the furan ring to reductive conditions. The equipment costs, together with concerns from the ecological and safety point of view, still hamper its production, therefore, novel synthesis routes need to be explored. Reductive amination has been recently demonstrated in the literature by employing electrocatalysis, thus providing novel insights into chemical catalysts-free amination [111]. However, biocatalysis is an attractive approach and offers the great advantage of enantioselectivity in mild reaction conditions. One-pot selective synthesis of optically pure amines from furan bio-based derivatives is a prerequisite for establishing novel enzymatic routes with significant commercial value and eliminating the production costs in this highly challenging area of research.

Transaminases (EC 2.6.1.18) are highly attractive versatile enzymes that catalyze the transformation of aldehydes and ketones towards the synthesis of chiral amines. These biocatalysts can provide a sustainable, high-yield, selective route to amines under mild aqueous conditions, by transfer of an amino group from a donor substrate to an acceptor compound. They have been used for the amination of FA and derivatives to produce furfurylamines [112], while the high-potential of this family of enzymes in industrial biotransformation processes is demonstrated by Merck's biosynthesis of the antidiabetic drug Sitagliptin [113]. Reductive amination of furans is possible both for HMF and FA as starting materials. Both aldehyde groups can be substituted with primary amines to generate amides with the use of transaminases. Transaminases have been reported to hold a primary role in the one-step biotransformation of furans (Figure 4) towards the production of furfurylamines with multiple applications.

There has been a limited amount of research on transaminases and furan derivatives, although highly promising and challenging. In the pioneering work by [112], the authors demonstrate the potential of different bacterial transaminases with varying enantioselectivities to convert furans to their corresponding amines, utilizing isopropylamine as a low-cost amine donor, at ambient temperature (30 °C). The results of this study show that enzymes from *Chromobacterium violaceum, Arthrobacter* sp. and *Mycobacterium vanbaalenii* were able to transfer amino groups not only to FA, HMF, FFCA and DFF, but also to various furan compounds and halogenated FAs, producing mono- and di-amines with yields that reach >90% for HMF, FA and FFCA and 70% for DFF. Apart from isopropylamine, alanine can also serve as an amine donor. In another study, a transaminase from *Vibrio fluvialis* was employed for the reduction amination of HMF with alanine as an amine donor, while an alanine dehydrogenase was added in order to shift the equilibrium [107]. A salt-tolerant ω-transaminase capable of catalyzing the amination of FA in salt water was studied [114]. The enzyme, produced by a halophilic bacterium *Halomonas* sp. CSM-2, exhibited 53.6% conversion of FA with (*S*)-methylbenzylamine as amino donor in a pH 9.0 seawater system; that yield was higher than its performance in freshwater. These results are quite promising, since there is a tendency for biorefineries in coastal areas to utilize seawater in order to cope with freshwater depletion. Transaminases have also been used together with lipases towards the production of optically pure substituted furfurylamines as functionalized building blocks [115].

Despite the high conversion yield, transaminases often suffer from low stability, which leads to many adverse effects when it comes to an industrial process. Immobilization has been used as an attractive option, as immobilized transaminases have shown increased thermal stability [116]. Moreover, immobilization offers fast recovery and reuse of the enzyme, as well as a simpler and less costly final product purification. In a work by [117], HMFA was synthesized by amination transfer reaction of HMF, which was catalysed by immobilized transaminase enzymes. Authors performed screening of a set of commercially available transaminases and achieved >99% conversion and reuse of the enzyme. Computational approaches constitute another attractive method in order to predict and design mutations of enzyme amino acids towards the stabilization of the subunit interface [118]. Transaminases, which are typically homodimers, are likely to be subjected to inactivation by subunit dissociation and local unfolding. This can lead to loss of the enzyme cofactor (pyridoxal 5'-phosphate),

which serves as a molecular shuttle to transfer an amino group from a donor (amine, amino acid) to an acceptor (ketone, aldehyde, keto acid). Folding energy calculations together with molecular dynamics simulation have been used to design surface and interface modifications; the produced mutants have shown higher activity, enhanced co-solvent compatibility and overall increased stability at their new elevated optimal temperature of action [118].

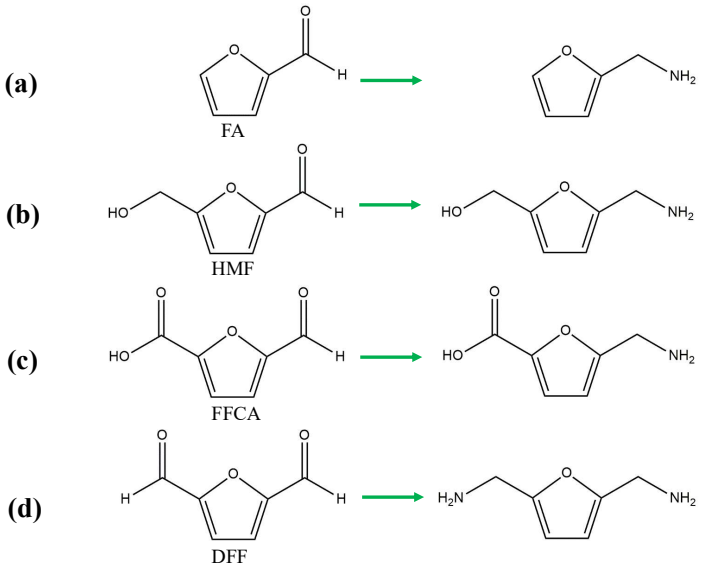

Figure 4. Schematic representation of furan-derivatives that have been reported in the literature to be transformed by aminotransferases to their corresponding amines [112,113,117]. (**a**) HMF to HMFA, (**b**) FA to FFA, (**c**) FFCA and (**d**) DFF to monoamine and diamine respectively. **HMF**: 5-hydroxymethylfurfural, **DFF**: furan-2,5-dicarbaldehyde, **FFCA**: 2,5-formylfurancarboxylic acid, **FA**: furfural, 2-furaldehyde.

A rising class of enzymes for amine synthesis are amine dehydrogenases (EC 1.4.99.3) [119]. Similar to transaminases, they can efficiently catalyze asymmetrically the reductive amination of chiral aldehydes and ketones, reaching up to 100% yield, albeit exhibiting a different mode of action than transaminases. Amine dehydrogenases are not strongly inhibited by neither the substrate nor the final product, such as transaminases, and they require a cheap nitrogen donor (NH_3) for their action. However, they exhibit lower enantioselectivity than transaminases, while cofactor regeneration is required. An amine dehydrogenase (a variant of the wild-type enzyme of *Bacillus badius*) was used for the efficient amination of a range of diverse aromatic and aliphatic ketones and aldehydes [120]. The enzyme showed high stereoselectivity in the amination of prochiral ketones, reaching amines with >99% optical purity, underlining the potential of these enzymes for amination reactions. Although amine dehydrogenases are promising candidates, currently there are no reports in the literature demonstrating the action of amine dehydrogenases on furans.

3.3. Reduction to Furan Alcohols

Furan alcohols, such as *2-(hydroxymethyl)furan (furfuryl alcohol, FOL)* and *2,5-bis(hydroxymethyl)furan (BHMF)* that originate from FA and HMF, respectively, (Figure 5), are used as starting materials in the synthesis of biopolymers [121]. BHMF is a versatile building block in the synthesis of polymers, fuels, and macrocycle polyethers; this molecule is further converted to *5,5′-dihydroxymethyl-furoin (DHMF)*, which undergoes enzymatic polycodensation reactions catalyzed by lipase towards aliphatic–aromatic oligoesters [122].

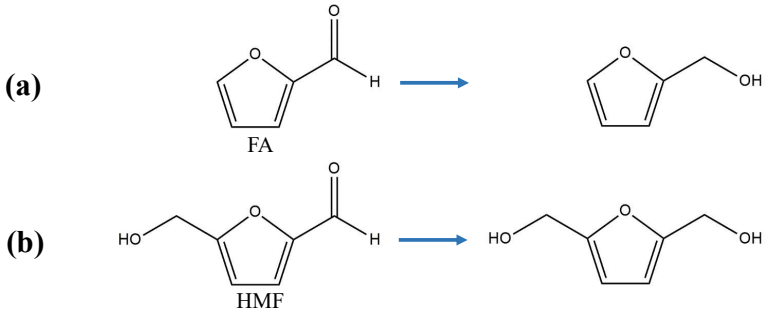

Figure 5. Schematic representation of furan-alcohol derivatives from (**a**) FA and (**b**) HMF that are have been reported in the literature and are catalyzed by alcohol dehydrogenases. **HMF**: 5-hydroxymethylfurfural, **FA**: furfural, 2-furaldehyde.

For the reduction of the furan keto-group into an alcohol, alcohol dehydrogenases (ketoreductases, ADHs, EC 1.1.1.1) have been investigated. The ADH from *Lactobacillus kefir* (Lk-ADH) is a well-studied enzyme with a broad substrate range [123]. This biocatalyst has been successfully implemented in a three-step enzymatic redox cascade to produce lactones from α, β-unsaturated alcohols in vitro [124]. Redox enzymes, such as ADHs, often require cofactors (NADPH/NADP+) that are continuously consumed during product formation. However, by implementing a regeneration system, the cofactor can be reused, and addition of expensive cofactors can thus be kept at a minimum, ensuring higher yield at reduced costs. For instance, adding glucose and glucose dehydrogenase (GDH) for the regeneration of NADPH by reduction of NADP+ represents a strategy frequently employed in the pharmaceutical and chemical industries [125].

HMF and FA conversion to BHMF and FOL, respectively, have been both reported to be catalyzed by whole cells, however ADH has been identified as the main enzyme implied in these biotransformation reactions. Many fungal and bacterial strains are widely known for detoxification of furan compounds with aryl alcohol oxidases and dehydrogenases [126], including *Pseudomonas putida*, *Saccharomyces cerevisiae*, *Amorphotheca resinae* that have been shown metabolize FA by conjugated reduction and oxidation reactions [127]. Moreover, the reduction of furans to corresponding furan alcohols has been demonstrated for *Pichia stipites*, and *Bacillus coagulans* under anaerobic conditions, providing the basis for the production of FOL through biotransformation [94,128]. The first study of the properties of an enzyme that catalyzes the conversion of FA was reported by Gutiérrez et al. [129]; in that study, a FA reductase (FFR) was purified from an *E. coli* strain and was used to reduce FA to FOL. In 2011, Li et al. reported a furfural reductase (FurX) from *Cupriavidus necator,* belonging in the Zn-dependent alcohol dehydrogenase family, that efficiently produced FOL from FA [130]. The sequence of this reductase was used as a model gene to seek for homologues, coming up with three ADHs, one from yeast (YADH1), one from *E. coli* (EcADH) and one from *Pseudomonas aeruginosa* (PaADH); all enzymes showed ADH activity on FA to produce FOL [131]. ADHs from *Cupriavidus basilensis* and *P. putida* have been identified for the NADH-dependent reduction of FA and HMF to the corresponding alcohols [94,132,133], while a variety of other bacterial enzymes act in the presence of either ethanol or NADH as electron donors.

Recently, a novel HMF-tolerant yeast strain *Meyerozyma guilliermondii* was isolated and was used for bio-catalytic whole-cell reduction of HMF into BHMF [134], with a high BHMF yield of 86% and excellent selectivity of >99%. He et al. reported a chemo-enzymatic conversion of biomass-derived xylose to FA by sequential acid catalyzed dehydration combined with reduction by recombinant *E. coli* cells harboring a NADH-dependent reductase, which was able to catalyze the bioreduction of FA to FOL [135]. The two processes were successfully combined to convert the xylose-rich hydrolysate to FA, and then to FOL with 44% yield based on the starting material xylose (100% FOL yield for the bioreduction step). Finally, recycling experiments for the carrageenan immobilized whole-cell and solid acid catalyst in one-pot FOL production are conducted; both catalysts showed excellent recyclability and no obvious decrease in activity was detected after five cycles of reaction.

ADHs from *M. guilliermondii*, heterologously produced in yeast have been reported for the reduction of HMF to produce BHMF with a high yield of 94% conversion and 99% selectivity within 24 h. For the first time, corncob hydrolysate was proposed as a cheap alternative to glucose as co-substrate for biocatalytic synthesis of BHMF, thus resulting in a significantly reduced production cost [131]. Various ADHs from yeast are capable of catalyzing FA reduction at the expense of ethanol [136]. To increase the catalytic activity and thermostability, protein engineering of ADHs has been investigated. Novel enzymes have been generated and were proved to be more effective towards the reduction of desired carbonyl substrates, with increased regioselectivity for furan substrates [137,138].

3.4. Other Enzymatic Activities and Future Perspectives

Different furan-based monomers described above can serve as starting materials for the synthesis of different compounds with unique chemical properties and different applications. These synthetic routes involve multiple steps and combine chemical catalysis with enzymatic reactions. Biocatalysts hold a key role in these transformations, offering a great selectivity in mild reaction conditions. As an example, a wide range of polyamides and polyesters can be produced by lipases and proteases, thus paving the way for furan valorization via enzymes [139]. Epoxides, another class of valuable versatile intermediate compounds, can undergo various reactions such as nucleophilic substitution and hydrolysis reactions, thus producing a repertoire of products [140,141]. Several scientific groups have reported the chemistry of epoxidation reactions and highlighted the role of the epoxide ring-opening process in synthetic reactions. The furanic compounds functionalized with epoxide groups can be used for bonding polycarbonate by cationic photo-curing and other compounds having a phenyl ring to prepare adhesives due to their rigid structure and hydrophobic property. Furanic diglycidyl esters from FDCA represent a viable bio-based alternative to their petrochemical aromatic counterpart [142]. Although the addition of epoxide groups has been reported by employing chemical steps, the use of enzymes for these transformations remains an undiscovered field of study. Apart from epoxy-functionalization, furan ring epoxidation can lead to rearrangement and ring opening, thus producing activated monomers, providing novel perspectives for synthesis. It has been reported that furan is oxidized by cytochrome P450 enzymes to the activated monomer metabolite cis-2-butene-1,4-diol [143]. P450 epoxidases contain a heme coenzyme that allows the addition of oxygen atom from O_2 to the alkene double bond [144], catalyzing epoxidations generating reactive electrophiles [145]. Oxidation of furan by P450 has been proposed to lead either to an epoxide-1 or a cis-enedione as epoxide intermediates [146]. Another class of enzymes that has recently attracted much attention and catalyze oxy-functionalization reactions are peroxygenases, as they combine the versatility of P450 monooxygenases with the simplicity of cofactor-independent enzymes, albeit with lower selectivity [147]. Regarding furan transformations, it is possible that upon addition of enzymes such as peroxygenases or P450 cytochrome monooxygenases, furan derivatives can undergo epoxidation and epoxide ring opening, thus forming reactive epoxide metabolites. After rearrangement, HMF–epoxide derivatives are transformed to tricarbonyl metabolites and this can be a possible route towards the synthesis of maleic acid or other compounds from furans. Synthesis of maleic acid has been reported to occur through a FA epoxide monomer [148]. For the biotransformation and enrichment of targeted bio-bricks, as well as their functionalization into activated monomers, selective oxidative biocatalysts with high specific activities are required. By expanding the use of enzymes, combining discovery of novel enzyme activities or design catalysts with desired properties, innovative processes can be developed towards the production of bio-based monomers and reactive compounds.

4. Conclusions and Future Prospects

Lignocellulosic biomass has been in the center of attention throughout the years as a feedstock for the production of second-generation biofuels. Recently, there has been a trend to extend the range of products that can be derived from biomass on behalf of the biorefinery concept, focusing on chemicals that can be utilized as starting materials for the production of polymers. By shifting

the interest towards furans, which are otherwise viewed as inhibitors to the valorization process, it is possible to combine a renewable source together with biocatalysis in order to create an environmentally friendly process to boost the production of bio-based polymers. The main aspect for the development of such processes lies in the conjunction of physicochemical processes with biocatalysis. An efficient fractionation method will allow for obtaining pure biomass fractions that can be easily processed downstream. The investigation and development of novel, robust biocatalysts with high activity and stability is the main challenge for the subsequent biotransformation of furans. Biocatalysts require high selectivity, in order to eliminate the formation of byproducts and boost the reaction yield, while the overall process has to be economically viable. The latter can achieved by employing a cost-effective strategy for the production of enzymes, together with immobilization and recycling.

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Abbreviations:

HMF: 5-hydroxymethylfurfural, **DFF**: furan-2,5-dicarbaldehyde, **HMFCA**: 5-hydroxymethyl-2-furancarboxylic acid, **FFCA**: 2,5-formylfurancarboxylic acid, **FDCA**: 2,5-furandicarboxylic acid, **HMFA**: 5-(hydroxymethyl) furfurylamine, **BHMF**: 2,5-bis(hydroxymethyl)furan, **FA**: furfural, 2-furaldehyde, **FCA**: 2-furancarboxylic acid or furoic acid, **FFA**: 2-furfurylamine, **FOL**: 2-(hydroxymethyl)furan.

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