Chapter 4
Subproducts and Inhibitors

In order for the conversion of lignocellulosic biomass to biofuels to be efficient, the use of pretreatments of the raw materials is fundamental to transform stable lignocellulosic structures, overcoming the recalcitrance of lignocelluloses, chemical composition, and digestibility in soluble sugars, thereby improving the subsequent process of fermentation [1–3]. As seen in the previous sections, there are several types of pretreatments (biological, physical, chemical) as well as the possibility of combining these. Nevertheless, some of the approaches used may suffer from significant disadvantages in terms of economic production, industrial scales, and ecological impacts [4].

Lignocellulosic resources avoid competition with food agriculture and are very abundant, reducing the costs of raw materials, because they can be obtained from a wide range of agricultural, forestry, and energy crop residues [5]. The action of pretreatments in this type of biomass can trigger a series of undesirable products and by-products that need to be evaluated and monitored when the objective is the production of biofuels and enzymatic production (Fig. 4.1). Often, the choice of the appropriate type of pretreatment should consider not only the transformation efficiency of the complex structures, but also the generation of by-products and inhibitors that interfere with the metabolism of microorganisms in the stages of hydrolysis and fermentation by which the bioconversion happens.

Bellido et al. [6] found that the concentration and composition of inhibitors formed are influenced by the types of raw materials used and the intensity of the pretreatment employed. Jönsson and Martín [7] reported that, in addition to chemical differences in raw materials, inhibition problems are often more significant because by-products accumulate via water recirculation and the high solid loads that are used to obtain the concentrated sugar.

In this section, we will present the generation processes for inhibitors associated with pretreatments to be applied to the residual biomasses. We will also discuss the existing models for the removal of these undesirable compounds and the interest of their application for other purposes, allowing added value of the by-product. We will

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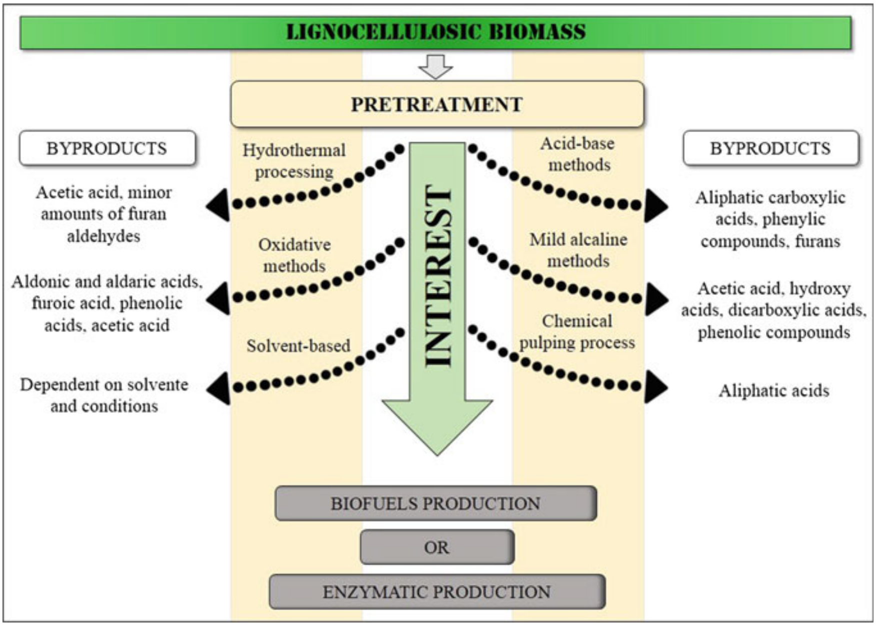

Fig. 4.1 Schematization of the main by-products and inhibitors formed from the use of pretreatments of residual lignocellulosic biomass. *Source* Authors

also discuss the major challenges and the major advances in this important stage that precede the hydrolytic and fermentative processes, as well as the enzymatic production.

4.1 By-products and Inhibitors from Physical and Chemical Pretreatments

Pretreatments such as acid hydrolysis, steam blasting, and ammonia expansion on lignocellulosic materials produce a number of inhibitors because of the severity with which they are applied to promote fiber rupture. Chandra et al. [8] analyzed the various characteristics of the lignocellulosic substrate at the level of fibers, fibrils, and microfibrils that were modified during pretreatment. They found that the initial characteristics of the biomass and the pretreatment applied played significant roles in the properties of the substrate that in turn governed the effectiveness of the enzymatic hydrolysis. The use of ammonia fiber expansion, for example, facilitated cellulose hydrolysis by cellulase, but generated amide inhibitors such as feruloyl amide derived by ferulic acid that attack biofuel models, while presenting new potential biological properties [9–11].

Most of the unwanted by-products present after pretreatment comprise three major groups: dehydrated sugar monomers (furans), degraded lignin polymers (phenols), and small organic acids [12].

4.1.1 Furans

By-products such as 5-(hydroxymethyl)-2-furaldehyde (5-HMF) and furan-2-carbaldehyde (furfural) are the major degradation compounds of xylose and glucose, respectively [13, 14]. In addition to these, various other products such as aldehydes and aliphatic and aromatic acids can also be formed by producing an inhibitory action on enzymes and yeasts (Fig. 4.1) [14].

Pretreatments with high temperatures and high acid concentrations are commonly used to promote the removal of lignin in the structure and convert the hemicellulose into simple sugars such as xylose, arabinose, lactose, and mannose [15]. These characteristics are the main factors related to the formation of undesirable compounds such as furans [16–20]. Together with the characteristics of this type of pretreatment, the amount of the carbon atoms in the monomeric sugar structures has influence on the type of compound formed, because 5-HMF may be the result of the dehydration of hexoses (six carbon molecules) and furfural, resulting from the dehydration of pentoses (five carbon molecules) [12]. At least, four routes for the formation of HMF from glucose and three routes for the formation of furfural from xylose are possible [14]. However, under neutral and basic conditions, the degradation of these sugars occurs through alternative routes [19].

The high concentration of furans mixed with other compounds in the same system as acetic acid, furfural, and lignin derivatives can be harmful to microbial growth and cause losses in the fermentation response [21]. It was found that the synergistic combination of acetic acid, furfural, and lignin derivatives resulted in greater decreases in ethanol yield and productivity than caused by the combined inhibition of single compounds [22]. In fermentations involving ethanol production, furfural may be more toxic than HMF, promoting the inhibition of enzymes acting on carbon catalysis, including acetaldehyde dehydrogenase, alcohol dehydrogenase, aldehyde dehydrogenase, glyceraldehyde 3-phosphate dehydrogenase, and pyruvate dehydrogenase [23]. It was also found that 2.0 g L^{-1} furfural, 2.0 g L^{-1} HMF, and 3.0 g L^{-1} acetic acid formed after acid treatment were sufficient to compromise the efficiency of fermentation [13]. A study showed that the production of furfural was lower with the use of dilute organic acids such as fumaric acid and maleic acid than with sulfuric acid (most commonly used) [24].

The choice of alkaline pretreatment methods such as wet oxidation and AFEX that are carried out at high pH may result in the formation of relatively low furan compounds [12]. In general, AFEX degradation products increase metabolic yield by reducing formation of fermentation by-products [10].

Furans are probably the most undesirable group of inhibitors, because the fermentability of hydrolysates obtained by acidification is inversely related to the concentration of these compounds [25]. Most of the time, the concentrated acid must be recovered from the system in order to make the process economically viable. In some cases, enzymatic hydrolysis can be avoided because the acid itself hydrolyzes the biomass into fermentable sugars [26].

Technological innovations such as the use of molecular dynamics simulations and quantum dynamics modeling along with experimental evidence of various mechanisms of degradation of monosaccharides in furans suggest that the formation of products can be controlled by adjusting process parameters [14]. This idea generated strategies to form efficient industrial processes that are more attractive with minimization of inhibitory by-products such as furans.

The choice of hydrothermal and alkaline pretreatment methods such as wet oxidation and AFEX that are performed at high pH may result in the relatively low formation of furanic compounds (Fig. 4.1) [27, 28]. In general, AFEX degradation products increase metabolic yield by reducing formation of fermentation by-products [10].

4.1.2 Phenolic Compounds

Formation of phenolic compounds is associated with the molecular weight, polarity, and side-chain characteristics of the lignin structure as well as the influence of some types of pretreatments applied in the lignocellulosic biomass, among which are acidic, basic, mild alkaline, and oxidative methods (Fig. 4.1) [7, 21]. The great problem with the presence of these compounds after the pretreatment of the biomass is the precipitation and strong irreversible inhibition that they cause in the enzymes [29]. Studies have shown that high concentrations of phenolic compounds present after acid treatment cannot be exclusively attributed to lignin breakage [30]. Phenols produced under alkaline conditions exhibit very high reactivity due to the ionization of hydroxyl groups [31]. Michelin et al. [32] evaluated the effect of phenolic compounds of pretreated sugarcane bagasse in liquid hot water (180–200 °C) on cellulolytic and hemicellulolytic activities. The effect of this pretreatment technique solubilized hemicellulose, acetic acid, and sugar oligomers from lignocellulose, while simultaneously solubilizing the phenolic compounds. Phenolic compounds inhibit cellulolytic enzymes and increase the pretreatment severity with liquid hot water, causing the solubilization of phenolic compounds to increase [29, 32]. In addition to the degradation of lignin, these compounds may be derived from phenolic ester groups associated with hemicellulose [33]. In addition, phenolic compounds are capable of promoting loss of integrity in biological membranes, reducing cell growth, affecting the ability to serve as barriers and enzymatic matrices, decreasing the assimilation of sugars, and interfering with protein synthesis by breaking DNA and inhibiting RNA [34, 35]. DNA damage may be associated with the formation of reactive oxygen species because it has a high positive charge on one side of the aldehyde group, especially if this group is bound to the next carbon with a double bond [36].

Studies have shown that phenols produced during pretreatment of sugarcane bagasse through wet oxidation are intermediate compounds during the process, because they are reactive and can condense to a greater extent during pretreatment to form carboxylic acids [30, 37]. The concentration of total phenolic compounds was higher under acid pretreatment conditions than under alkaline conditions. The most abundant phenols are derived from G units (vanillin, vanillic acid, acetovanillone, vanillyl alcohol, guaiacol, and homovanillic acid), S units (syringaldehyde, syringic acid, acetosyringone, and syringol), and H units (p-hydroxybenzaldehyde, p-hydroxybenzoic acid, p-hydroxyacetophenone, and p-hydroxybenzyl alcohol) [30]. Some of these, including 4-hydroxybenzaldehyde, vanillin, syringaldehyde, acetosyringone, vanillic acid, syringic acid, and (4-hydroxy-3,5-dimethoxyacetophenone), were found in wheat straw pretreated with alkaline wet oxidation in the range 0.04–0.12 g 100 g_{straw}^{-1} [37].

In addition to phenolic compounds, some non-phenolic but aromatic compounds can be found in pretreated lignocellulosic hydrolysates [7]. Among the most frequent are benzoic acid [38, 39], para- and ortho-toluic acid [19], benzyl alcohol [39], cinnamic acid [40], cinnamaldehyde [41], and 3,4-dimethoxycinnamic acid [39]. The reason that some of the respective acids are clustered in the phenolic groups, and not in aliphatic carboxylic acid groups, is explained by the fact that they have phenylpropanoid structures, suggesting that they originate from lignin or from the hydrolysis of esterified phenols. They are generally found at low concentrations in the lignocellulosic hydrolysates, and the inhibitory effect becomes more potent than the aliphatic carboxylic acid species [7].

Rasmussen et al. [42] discovered and quantified 28 oligophenolic inhibitors of cellulase hydrothermal pretreatment of wheat straw biomass. The authors suggested that pentoses are directly involved in the formation of compounds and proposed that the hydrothermal pretreatment contributes to the formation via reactions with autocondensation of pentoses involving aldol condensations, 1,4 additions to α, β unsaturated carbonyl compounds, decarboxylation, and oxidation of 3-ketoacid. Xylose is the precursor in the reaction pathways for the formation of these inhibitors, and many may still trigger the formation of pseudo-lignin. Therefore, protecting the reactive anomeric center of xylose could reduce the formation of inhibitors. The process of protection of the reactive anomeric center was carried out by the authors using ethylene glycol ether together with hydrothermal pretreatment, effectively reducing the level of oligo-phenols by 73%. That study provided a new way to develop reactions that hinder the formation of inhibitors of the lignocellulosic source [42]. Nevertheless, technological improvement is still required for recovery of xylose and separation of ethylene glycol monobutyl ether from the aqueous reaction mixture [42].

The occurrence of p-hydroxyphenyl derivatives after pretreatment techniques can be attributed to the lignin solubilization of the secondary wall of lignocellulosic biomasses that is rich in p-hydroxyphenyl units [30, 43]. The existence of p-coumaric acid in the cell wall as a non-constitutional part of the lignins may undergo oxidative pretreatment and may be one of the reasons for the formation of p-hydroxyphenyl derivative compounds [30].

Other types of pretreatments have been associated with the formation of these compounds. Steam blasting can trigger the generation of syringaldehyde, 4-hydroxybenzaldehyde, and vanillin [44]. Dry pretreatments (AFEX and pretreatment with ethylenediamine) may even reduce water consumption, while increasing the concentrations of soluble phenolics for enzymatic hydrolysis [45, 46]. Hydrothermal processes based on hot water pretreatment release phenolic compounds that affect β-glycosidase or β-xylosidase components of the enzyme cellulase and hemicellulose [32].

4.1.3 Organic Acids

Acetic acid is a by-product of the cleavage of acetylated groups present in hemicellulose during thermal and chemical pretreatments [19], including acid pretreatment [13]. For example, acetyl and uronic acid groups may be present at the 2′ and 3′ position of sugar in wheat straw residues [47]. In other cases, with the use of hydrothermal pretreatment of the biomass, the formation of acetic acid can occur by means of acetylated galactoglucomannans that result from hydrolytic cleavage of the acetyl substitutions during pretreatment of acetylic bonds in xylan [14]. Acetic acid, although considered a small organic acid, is the most abundant in most cases. In addition to acetic acid, uronic acids, formic acid, and levulinic acid can also be formed from the degradation of sugars such as xylose and glucose [7, 13] and degradation of HMF and furfural [48]. In wet oxidation, monomeric sugar molecules can be oxidized to formic acid and acetic acid [37]. Pretreatments with organic acids can fractionate the lignocellulosic biomass in cellulosic solid (greater than 85% cellulose and lignin contents below 10%), hemicellulosic syrup, and high-purity lignin. However, the delignification process triggered an acylated (acetylated or formylated) cellulose. The presence of the acetyl group and its degree of acylation may increase the cellulose chain diameter, limit the enzymatic hydrolysis of cellulose, and also impair the recognition of the cellulase enzyme for this substrate [49–51].

Levulinic acid was produced under strongly acid pretreatment conditions, while negligible concentrations were produced at higher pH. This trend was similar to the previously reported 5-HMF and furfural productions. The most likely explanation for this phenomenon is that levulinic acid is formed after further degradation of 5-HMF under strongly acidic conditions [19, 48, 52]. Formic, acetic, and levulinic acids were also detected after pretreatment by steam explosion on cellulosic material; it was observed that, after the rinsing of the treated raw material, formic acid and levulinic acid affected the activity of cellulase enzymes [44]. Other studies also reported that severe pretreatment conditions with steam explosion generate inhibitors such as aromatic compounds and dehydration by-products such as weak acids and their weak derivatives that influence subsequent hydrolysis processes [53–56]. Recent studies that verified the potential of corn straw in methane production suggested that the inhibition caused by the rigorous pretreatment conditions of steam explosion may be due to the formation of pseudo-lignin; high lignin contents that are present in the pretreated material affect methane yield [57]. One of the reasons found for the formation of pseudo-lignin with severe explosion conditions may involve condensation and re-polymerization reactions that lead to increased acid-insoluble lignin fractions

[57, 58]. One of the ways to minimize the generation of inhibitory compounds and improve the efficiency of vapor explosion pretreatment is the addition of catalysts such as H_2SO_4, H_3PO_4, SO_2, or CO_2 [59–62]. However, this effect combined with the high severity also affects the formation of inhibitors such as carboxylic acids (acetic acid, formic, among others), as well as aromatic aldehydes (5-HMF, furfural, phenols) (Fig. 4.1) [62].

In ethanol fermentations, the use of combined severity (CS), consisting of a single parameter involving residence time, temperature, and sulfuric acid concentration as pretreatment conditions, showed that the additional increase of CS and formation of formic and levulinic acid simultaneously increased along with increased yields of mannose and glucose under these conditions [63].

As seen so far, acid pretreatment of biomasses is thought to be one of the most critical in the formation of inhibitory by-products. In addition to furan aldehydes and phenyl aldehydes, it is likely that small aliphatic aldehydes are also ubiquitous in biomass after this type of pretreatment [64]. Even though they are considered volatile compounds and are easy to vaporize, more research should be needed to understand the meaning of the aliphatic aldehydes present in this system [7].

A recent study applied data modeling to systematically evaluate the prediction of the inhibitors present in the pretreated lignocellulosic biomass in the fermentation of bioethanol using the yeast *Saccharomyces cerevisiae*. With the objective of reducing experimental costs, the authors used mathematical models of nineteen representative inhibitors in the fermentation of bioethanol individually and in combination. According to the authors, this was an innovative methodology to evaluate inhibition and to eliminate the stronger inhibitors that exist in pretreated lignocellulosic hydrolysates [3].

4.2 Oxidative Pretreatments: From Challenges to Trends

Oxidative pretreatments have been shown to be effective in making the solid cellulose fraction more accessible for enzymatic hydrolysis and fermentation. These methods include wet oxidation and oxidative lime with liquid hot water [19, 65, 66]. The combination of wet oxidation with alkaline compounds minimizes the formation of furanic and phenolic aldehydes [7].

Among the alternatives to existing pretreatments, ozonolysis is one of the most promising methods of oxidative pretreatments of lignocellulosic biomass for the degradation of lignin, generating reduced effects on hemicellulose and cellulose. Its mode of action is preferentially on the structure of lignin because the deficiency of electrons in the terminal oxygen causes its action to be in an electron-rich substrate such as lignin that presents many more electrons than do other carbohydrates [67]. For applications that require the use of delignified biomass such as biofuels (biogas, bioethanol, butanol, biohydrogen) and even the production of enzymes, the use of this method is compelling [68].

The challenges that are encountered in prior processes such as high generation of inhibitors during pretreatment processes are minimized with this technology. Furfural and HMF, commonly found as sugar-degrading compounds, are not detected. However, ozonolysis during the degradation of sugar generates mainly oxalic acid, formic acid, acetic acid, and levulinic acid [67, 69]. For all processes of treatment of lignocellulosic biomass using O_3, acetic acid is a by-product. This does not have to be considered a serious problem, because acetic acid can be converted to biogas that may be used for the production of heat and electricity [70].

Ozonolysis for the pretreatment of sugarcane bagasse generated acetic acid, formic acid, lactic acid, and xylitol, however, at lower concentrations than other published pretreatments of sugarcane [68].

The inhibitory effect of carboxylic acids is directly related to pH. For these compounds to penetrate the cell membrane of microorganisms, they must be present in a no dissociable form. Because intracellular pH is commonly higher, there is dissociation of carboxylic acids, leading to decreased internal pH, consequently affecting cellular functions. For subsequent hydrolysis and fermentation processes not to be affected, it is proposed that this form of pretreatment could be improved with increasing pH [67].

One of the great challenges that this method must overcome is scaling-up. Nevertheless, technological advances are reducing costs for ozone production by increasing prospects for application in the near future [70].

4.3 From Biological Methods

Phenolic compounds, furan derivatives, and weak acids are toxic inhibitors formed after the application of chemical, physical, and physicochemical pretreatments that must be removed in an additional stage of detoxification [71]. The formation of these inhibitors, in addition to causing disadvantages to hydrolysis, contributes to the corrosion of equipment that results in a compromise of the process. The use of biological pretreatments is an alternative because it reduces the additional steps of residual flows for detoxification and is considered an environmentally more promising model. Nevertheless, some disadvantages have been reported, including the need for longer durations of lignin degradation; furthermore, some of the cellulose and hemicellulose can be degraded [72, 73].

According to Carrillo-Nieves et al. [73], the goals of consolidated bioprocesses are as follows: to find a microorganism that has the capacity to promote rupture by means of enzymatic forms of lignin, avoiding the use of aggressive chemicals that subsequently need treatment; to tolerate the high inhibitory concentrations produced during the process; and to produce enzymes necessary to transform cellulose and hemicellulose into sugars.

Wang et al. [74] investigated a biological pretreatment of corn straw using ligninolytic enzymes and reported that the formation of microbial inhibitors was reduced with this technique.

4.4 Methods for Detoxification

Several methods of detoxification are used to remove toxic compounds from plant biomass hydrolysates, including enzymatic biological treatments (laccase), physical treatments, evaporation and extraction, chemical treatments with alkaline agents (NaOH, CaO, $Ca(OH)_2$), and physical–chemical treatments involving adsorption with activated carbon and ion-exchange resins [25].

According to Travaini et al. [67], in several publications, the use of washing water resulted in an effective phase of removal of inhibitory compounds, increasing glucose release after enzymatic hydrolysis when pretreatment with ozonolysis was used. In ozonated wheat straw washing water, Schultz-Jensen et al. [75] found various lignin degradation products, including phenolic carboxylic acids, phenolic, vanillic, acetic, citric, and other products.

Several methods to detoxify the culture medium can be used, including physical (detoxification-mediated), chemical (addition of $Ca(OH)_2$), adsorption (using activated carbon ion-exchange resins), and biological (microbial and enzymatic) to combat the inhibitors of xylitol production [76].

Cetoxification may also reduce the amount of sugars and consequently decrease the efficiency of fermentation [77]. Piotrowski et al. [11] showed that the search for new strains that decrease the inhibitory effects of degraded lignocellulosic biomass is an economically more favorable strategy than applying expensive detoxification methods that reduce the sugar content of biomass.

4.5 By-products and Inhibitors: A Form of Valorization

Given the great impasse that the by-products and inhibitors of the degradation of lignocellulosic materials cause in enzymatic production processes and biofuels, there is a need to search for solutions to add value to the by-product. Often, the purpose of a pretreatment is not to form monomeric sugars and raw materials for biofuel synthesis or enzymatic production, but rather to pay attention to the valorization advantages of other chemical compounds formed during pretreatment.

Furfural is a chemical solvent that has been used to separate saturated and unsaturated compounds in oil, gas, oil and diesel refining industries [78]. The aldehyde group present in the structure and the unsaturated bonds make this material a highly versatile compound for the production of a wide range of industrial chemicals, including plastics, pharmaceuticals, and agrochemicals [79]. The production of this compound involves the acid-catalyzed hydrolysis of the hemicellulosic biomass fractions of pentose (such as cornstalks and corncobs, oat and peanut husks, as well as other agricultural surpluses) and consecutive cyclodehydration of pentose monomers (xylose being the most predominant pentose in most feedstocks) [80].

HMF can be transformed into a number of compounds, including 5-ethoxymethyl furfural [81], 5-arylaminomethyl-2-furanmethanol, 5-hydroxymethylfuroic acid, furfuryl alcohol, levulinic acid, and levulinate esters [82]. 5-HMF and furfural derivatives also have the potential to replace petroleum-based chemicals and building blocks, offering more sustainable routes for the production of polymers, fuels, and fine chemicals [83].

According to Luo et al. [84], furfural production with high selectivity and productivity is a challenging but crucial process to alleviate dependence on petroleum-derived chemicals. The production of furfural with high selectivity and yield requires catalysts; organic solvents are the most common methods for the depolymerization of dissolved hemicellulose. In particular, the adjustment of biphasic systems of organic solvents and NaCl is a compelling choice to produce furfural because it avoids secondary reactions and the formation of undesirable compounds, directing the balance of the system exclusively toward the formation of furfural [84].

There are no synthetic routes available for the production of furfuraldehyde; it is exclusively produced from renewable biomass resources through acid-catalyzed dehydration of pentoses [85].

Value-added products can also be obtained from the conversion of lignin with the probability of offsetting the additional costs caused by pretreatment processes. The technologies of pretreatment provide refining of biomass, and further facilitating recovery of lignin, together with processes in engineering, will allow the use of biopolymers such as low-cost carbon fibers, plastics and thermoplastic elastomers, polymer foams, and other fungible fuels [86].

Lignin pretreatment processes that involve oxidative methods can trigger the formation of aromatic compounds and aldehydes that do not have much market value, because they contain aromatic rings. However, oxidation also results in open-ring organic acid productions that are more highly valued. Natural oxidative pretreatments, based on the depolymerization of lignin via oxidative enzymatic process with the use of laccases and peroxidases secreted by white-rot fungi, have been a new strategy for obtaining aromatic compounds of low molecular weight [86–89].

Carbon and energy storage compounds such as hydroxyalkanoate polyester, in this case polyhydroxybutyrate (PHB), present in alkaline pretreatment liquors, can be synthesized through aromatic rings by means of bacteria and may be comparable with the mechanical properties of petroleum-based plastics or in the pharmaceutical industry because of their biocompatibility and degree of polymerization. Studies in this area reinforce the notion that sustainable models in the context of biorefineries with enzyme-mediated supplementation strategies in synthesis processes can provide a more attractive economic outlook.

For some types of waste pretreatment methods, adjustments are made to allow a more affordable fraction of products with high added value. Phenolic compounds have wide use in food additives, the pharmaceutical and cosmetics industries, energies, diverse chemicals, and phenolic resins [90]. The residue of grape marc is a raw material with great potential that is a rich source of phenolic acids, anthocyanins, colored flavonoids, and tannins. The pretreatments of this material are aimed at extraction of phenolic compounds, lactic acid, xylitol, bioadsorbents, and oligosaccharides [91]. The extraction of phenolic compounds from this type of residue is a focus of study because of its compelling activities including antioxidants [91, 92].

To date, more than 90% of phenol production is derived from the synthesis of benzene, obtained from fossil fuels and triggering concern for the limitation of this resource and the aggravating factors of environmental pollution [93]. By contrast, production of phenol via the degradation of lignin is a method of manufacturing phenol from renewable raw material [94].

Studies of the role of phenolic compounds in the secondary metabolism of plants, including several biological functions, have associated the antioxidant properties of these substances with existing benefits such as healthy diets and prevention of chronic diseases through the consumption of fruits and vegetables rich in phenolic compounds [95, 96].

Phenolic compounds can also positively or negatively affect the sensory characteristics of foods, including color, taste, and astringency. This impact needs to be evaluated and becomes important so that health-promoting products are also palatable and are widely consumed [95]. In addition to antioxidant functions, phenolic compounds prevent diseases through other mechanisms, including cell signaling, gene expression, and modulation of enzymatic activity [97].

Although phenolic compounds can be transformed into high-value food additives, antioxidant recovery has not yet been achieved on an industrial scale [98]. One of the most valuable phenolic compounds resulting from lignin is vanillin, presenting good prospects in the polymer industries [99].

Levulinic acid, another compound that has received substantial attention in the preparation of pharmaceuticals, dyes, plastics, pesticides, additives, resins, and lubricating additives, is considered by the US Department of Energy to be among the 12 most valuable platform compounds [100]. Among other possible applications, upgrades of liquid fuels such as levulinic acid and methanol can produce methyl and ethyl esters under the action of acid catalysts [101]. In food, it can serve as a raw material for jasmine flavors. In addition, when mixed with 2-methyltetrahydrofuran, these compounds can also be added to gasoline (up to 70%) without the need for engine modification [101, 102].

Other modes of levulinic acid valorization, described by Li et al. [101], include the synthesis of pyridinyl levulinate, 2-methyl-3-indole acetic acid, pesticidal intermediates, 2-mercapto-4-methyl-5-thiazole acetic acid, and indomethacin pharmaceutical intermediates. In addition, calcium decanoate obtained by levulinic acid and calcium carbonate can be useful in the medical field for intravenous injections to maintain the excitability of muscles and nerves and to assist in bone formation. They can also be used in skin care products and cosmetics for the treatment of acne, sebum, and even as anti-inflammatory and antibacterial treatments [101].

The recovery of the liquid fraction after pretreatment by steam explosion and enzymatic hydrolysis of the lignocellulosic biomass was shown to be beneficial for biogas production, because the energy recovery can be associated with the digestibility of lignin inhibitors and polymers in the transformation of methane [5].

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