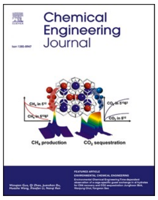
Chemical Engineering Journal 424 (2021) 130560

Contents lists available at ScienceDirect

Chemical Engineering Journal

journal homepage: www.elsevier.com/locate/cej



Inhibition and disinhibition of 5-hydroxymethylfurfural in anaerobic fermentation: A review

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ARTICLE INFO

Keywords:
Biomass
Biofuel
Inhibitor
Anaerobic digestion
Detoxification
5-hydroxymethylfurfural (HMF)

ABSTRACT

Anaerobic fermentation is a clean production process for recycling of many agricultural and industrial wastes. During anaerobic fermentation, the existence of various inhibitors often leads to low efficiency or even failure of anaerobic digesters. 5-hydroxymethylfurfural (HMF) is such an inhibitor which can be produced in the pretreatment of biomass for subsequent anaerobic digestion. This paper provides a review of various production methods of HMF and its effects on hydrogen production, methane production and ethanol production through fermentation. The conversion and removal of HMF were summarized from the aspects of biomass pretreatment, non-biological treatment and biological treatment. This article aims to provide new ideas and methods for reducing the inhibition effect of HMF on anaerobic fermentation of biomass and restoring the performance of the anaerobic fermentation.

1. Introduction

Currently, fossil fuels including coal, oil and natural gas are the major energy sources worldwide. The reserves of fossil fuels are limited, and the excessive exploitation and utilization of these energy resources produce a large amount of carbon dioxide, resulting in a severe impact on the environment [1,2]. Therefore, the research and development of renewable energy have become a worldwide focus; especially the research on second-generation biofuels, such as bioethanol, biohydrogen and biomethane [3]. According to the forecast of the United Nations Conference on Environment and Development (UNCED), the utilization of biomass resources will reach 50% of the total world resource utilization by 2050 [4]. However, numerous lignocelluloses have been discarded or burned directly [5].

Anaerobic fermentation refers to the degradation and transformation of organic matters, particularly, organic wastes by microorganisms under anaerobic conditions [6-11]. Biological hydrogen, biomethane and ethanol are produced through the fermentation and metabolisms of microorganisms. Pretreatment is usually used to increase yield before anaerobic fermentation [12].

There are many studies on the utilization of industrial and agricultural biomass wastes for the production of biofuels or other valuable chemicals [13-17]. Biomass contains cellulose, hemicellulose and lignin enhancing the tensile strength and the protection of the plant, and hindering microbial degradation [18]. In order to make better use of biomass, pretreatment is needed [19,20]. Pretreatment processes including physical, chemical, and biological ones have been investigated and used [21-23]. Since pretreatment is beneficial to increase yield and improve economic benefits, pretreatment plays a vital role in biomass utilization [24]. However, some of the intermediates and byproducts such as furfural, hydroxymethyl furfural (HMF), formic acid, and levulinic acid produced during pretreatment are inhibitors of subsequent anaerobic fermentation [12,18,25,26]. The concentration and type of these substances are closely related to the raw materials, pretreatment

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https://doi.org/10.1016/j.cej.2021.130560
Received 1 April 2021; Received in revised form 13 May 2021; Accepted 24 May 2021

methods and conditions.

HMF can be produced during the hydrolysis phase of anaerobic digestion by thermal and thermo-chemical pretreatments at low pH [27,28]. As a dehydrated product of hexose, HMF has two important functional groups, hydroxyl and aldehyde, and is a high value chemical from biomass [29]. HMF is a relatively unsaturated heterocyclic furan molecule, which can be replaced by hydroxide and aldehyde functional groups, oxidized to dicarboxylic acid or reduced to diol, and can be purified into fuel by hydrogenation [30]. Studies have reported that HMF inhibited hydrogen production, interfered with microbial growth, and had synergistic effects with other inhibitors [31-33]. High concentration of HMF in wastewater or anaerobic sludge could lead to the deterioration and even failure of anaerobic reactors [34].

Due to the important role HMF has played in anaerobic fermentation, numerous research articles are available on the production of HMF in anaerobic fermentation [35], the inhibitory effect of HMF [36], and the detoxification method of HMF [25]. However, few articles have rigorously discussed such research and put forward constructive insights. The generation of HMF in biomass utilization is described, firstly. Then, the effects of HMF on hydrogen production, methane production and ethanol production in anaerobic fermentation are reviewed with a focus on the inhibitive effect. Disinhibition measures are also summarized and commented for the offset of the HMF inhibition in anaerobic fermentation. Through the critical review of data on the influence of HMF in anaerobic fermentation we hope that a better optimization of anaerobic fermentation can be achieved.

2. Generation of HMF

Generally, most saccharides, including glucose, fructose, and cellulose, can be used as potential feedstock for the production of HMF [26]. When biomass is used to generate HMF, the crystal structure of cellulose in biomass must be destroyed by pretreatment in order to produce glucan first. The glucan is then hydrolyzed to glucose or others hexose. After that, the glucose is isomerized to fructose. The fructose continues to be dehydrated and eventually produces HMF [29,38,39]. The pathway for the conversion of biomass to HMF is shown in Fig. 1.

2.1. Generation of HMF using hexoses as feedstock

Recent studies on the generation of HMF in hexoses utilization are summarized in Table 1. The types of catalysts and experimental conditions are different, which is also the focus of our discussion. The catalyst plays an important role in the reaction selectivity and hexose conversion process; the function of Brønsted acid is mainly to catalyze the hydrolysis of glucan and promote the dehydration of hexose. Lewis acid catalyzes the polarization of the carbon group formed after opening the ring structure of glucose, which is beneficial to the process of isomerizing glucose to fructose. The most commonly used Brønsted acids are sulfuric acid, phosphoric acid, hydrochloric acid, oxalic acid, Lewis acid and p-toluenesulfonic acid. Basic catalysts usually cause side reactions, so Lewis acid is the first choice. In the past few years, various catalysts have been studied, such as metal oxides, sulfate or phosphate metal oxides, metal-doped zeolites and various other basic or Brønsted and Lewis acid catalysts. The catalysts should have protons or Lewis acid; the systems used in the reaction also include aqueous, organic, two-phase and ionic liquid systems. DMSO (dimethylsulfoxide): water, MIBK: water and THF (tetrahydrofuran): water was the most commonly used two-phase systems. [27,39-43,45,46].

In recent studies, it was found that a new type of heterogeneous catalyst made by adding Lewis or Brønsted acid sites to the surface of activated carbon prepared from lignocellulosic waste birch wood chips can effectively convert glucose into HMF. In the 160 °C biphasic water: THF system, the highest yield of hydroxymethyl furfural (51%) can be obtained in 8 h [40]. Zuo et al. [41] used $AlCl_3$ as a catalyst to directly synthesize bio-based furan products from bio-derived glucose under EtAc/water two-phase conditions. Under these conditions, the yield of HMF was 52.9%. Interestingly, Guo et al. [42] used $AlCl_3$ and HCl as

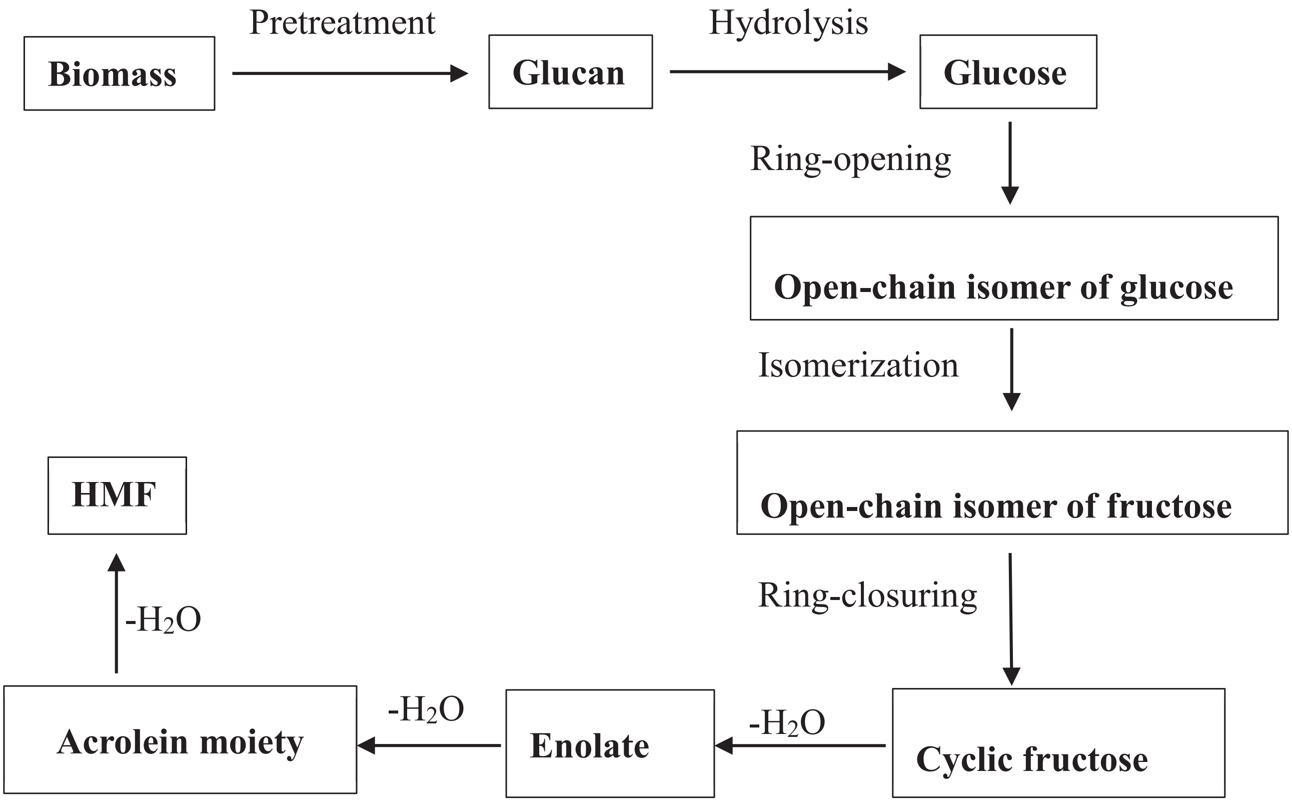

Fig. 1. Pathway for the conversion of biomass to HMF.

Table 1
Recent methods of catalytic conversion of biomass into HMF.

Substrate	Catalysts	Conditions	HMF Yields (%)	Conversions (%)	Refs.
Glucose	AACH	120 °C, 4 h, [BMIM]Cl, DMSO	52.17	83.59	[44]
Glucose	$CrCl_3·6H_2O$	120 °C, 4 h, [BMIM]Cl, DMSO	69.76	90.15	[44]
Fructose	HO_3S-POPs	140 °C, oil-bath, 5 mol % loading	60 ~ 70	90	[27]
Glucose	Al-SPFR	170 °C in 2 h, 0.1 g Al-SPFR and 0.1 g glucose	47.74	95	[45]
Glucose	$SnCl_4$	_	13.9	100	[46]
Glucose	$SnCl_2$	_	8.3	100	[46]
Fructose	Phosphoric	140 °C, 13 min, pH 1,	45	87	[47]
Fructose	Phosphoric	140 °C, 431 min, pH 2	44	88	[47]
Fructose	Citric	140 °C, 53 min, pH 1.4	42	78	[47]
Fructose	Glycolic	140 °C, 224 min, pH 1.8	42	88	[47]
Fructose	Acetic	140 °C, 243 min, pH 2	48	95	[47]
Fructose	Hydrochloric	140 °C, 22 min, pH 2	41	75	[47]
Glucose	SnP	glucose/catalyst 2.5:1 w/w, 175 °C, 1 h	61	98	[49]
Fructose	SGC650H	DMSO, 100 °C, 3 h	100	–	[48]
Glucose	Sulfanilic acid	160 °C, 30 min	44	–	[50]
Glucose	SAPO-34	170 °C, 40 min, 20 mg	93.6	100	[51]
Lignocellulose	$AlCl_3$	160 °C, 1.5 h, DES/MIBK	35.7%	–	[39]
Wood chips	$CrCl_3$·6H2O	120 °C, 2 h, [BMIM]Cl	79	–	[59]
Rice straw	$CrCl_3$·6H2O	60 °C, 24 h, [BMIM]Cl	76	–	[59]
Microcrystalline Cellulose	H_2SO_4	175 °C, 1 h, DMSO, H_2O	24.1	–	[35]
Cellulose	$TiO_2/ZrO_2/CO_2$	200 °C, 3 h, THF, H_2O	48.4	–	[60]
Mixed saccharide	$ZnSO_4$, $NaHSO_4$	160 °C, 1.5 h, THF, H_2O	40	–	[62]
Cellulose	Nb/C-50	160 °C, 4 h, THF, H_2O, NaCl	59.3	–	[64]

homogeneous catalysts and methyl isobutyl ketone as the organic phase to synthesize HMF from glucose in a slug flow capillary microreactor. They proposed this method to convert glucose into HMF more efficiently and sustainably, because the microreactor has excellent heat transfer efficiency, and the slug flow operation greatly promotes the mixing/reaction in the droplets and promotes the extraction of HMF in the organic slug, the yield of hydroxymethyl furfural is improved. extraction of HMF in the organic slug, the yield of hydroxymethyl furfural is improved. Recently, Le et al. [43] synthesized some sulfonated magnetic carbon nanoparticles (SMCNs) with good catalytic activity from eucalyptus oil. Under the optimal temperature and the most suitable reaction time, it can catalyze the conversion of fructose into HMF, the conversion rate of fructose can reach 84%, and the yield of HMF is 51.6%. Using ammonium aluminum carbonate hydroxide (AACH) or homogeneous acid catalysts as catalyst prepared via the hydrothermal synthetic, glucose can be efficiently converted into HMF in the mixed system of DMSO (dimethyl sulfoxide) and ionic liquid ([Bmim] + Cl–) [44]. Du et al. [27] synthesized a series of porous organic polymers functionalized by sulfonic acid (HO_3S-POPs) with different surface areas and porosity profiles through an aerogel template approach. The results showed these POPs, compared with some commercially acid resins, have good catalytic activity and selectivity in catalytic conversion of fructose into HMF. Zhang et al. [45] synthesized an $Al3^+$-modified formaldehyde-p-hydroxybenzenesulfonic acidic resin catalyst (Al-SPFR) to produce HMF. Marianou et al. [46] studied the effect of Brønsted and Lewis acidity on conversion of glucose into HMF in aqueous and organic media. In their study, different Sn-based catalysts had different roles, some were used as homogeneous catalysts or oxides, others act as ion-exchange cations. Körner et al. [47] stated the effect of conversion of fructose to HMF using different Brønsted acids on the hydrothermal. Interestingly, the type of acid used has however only a little effect on the maximal HMF yield. Tacacima et al. [48] demonstrated that high HMF selectivity and yield were obtained by using fructose as feed substrate under the catalytic dehydration by a gel-type strongly acidic resin (SGC650H). It is worth mentioning that the use of dimethylsulfoxide as a solvent can reduce the formation of by-products during the hydrolysis of fructose. Rao et al. [49] introduced a way to synthesize tin phosphate as catalysts, and these catalysts have good activity in the dehydration of glucose to HMF. Parveen and Upadhyayula [50] compared the catalytic mechanism and effects of three kinds of organic catalysts on glucose conversion to HMF. They found that Sulfanilic acid, which contains both sulfonic acid groups and the amino groups, is an effective multifunctnal catalyst. In addition, they claimed that the basic groups and the Bronsted acidic groups are respectively closely related to the isomerization of glucose and the catalytic dehydration of fructose. Zhang et al. [51] described a new catalytic approach to transform glucose to HMF by using SAPO-34 as catalyst and γ-valerolactone (GVL) as solvent. Furthermore, this method can convert glucose efficiently and has a high yield of HMF. The types of catalysts, experimental conditions, substrate conversion rates, and HMF yields in the above methods are summarized in Table 1.

In short, first of all, although the yield of HMF converted from fructose is higher than that of glucose, it is expensive and has a lower natural abundance, and only exists in food biomass such as sugar cane or corn. On the contrary, glucose is not only cheap, but also very abundant. Secondly, traditional homogeneous catalysts are difficult to recycle and easily cause corrosion. Some catalysts are poisonous and have high operating costs. Among them, the aluminum alkoxide compound is highly efficient, easy to use, and is a new type of catalyst that is less harmful to the environment. Heterogeneous catalysts are easy to recycle and have strong sustainability. Carbon nano-particles (CNP) and magnetic carbon nano-particles (MCN) prepared from activated carbon are new types of heterogeneous catalysts, which have excellent characteristics such as easy operation, large surface area, and effective functionalization. Finally, the two-phase system can continuously remove HMF from the reaction mixture, preventing rehydration reactions and increasing yield.

2.2. *Production of HMF using biomass wastes*

The utilization of biomass waste is a hot research topic. There are methods to directly use different biomass to produce HMF, and there are biomass utilization methods to use HMF as by-products. Recent studies on the generation of HMF in biomass waste utilization are summarized in Table 1.

Pham et al. [52] prepared a modified Al-MCM-41 solid acid with a molar ratio of silicon to aluminum as a catalyst to catalyze the conversion of cellulose to 5-hydroxymethylfurfural, with a 5-HMF yield of 40.56%. Studies have shown that acidic seawater can promote the conversion of biomass to HMF under microwave heating conditions. Surprisingly, in Jin et al. [53] research, it was found that cellulose formylated in an acetonitrile–water co-solvent system was catalyzed by maleic acid and aluminum chloride to show ultra-high reactivity and selectivity for HMF production. Chloride and lithium chloride have been reported to improve the conversion of biomass into 5-hydroxymethylfurfural and other value-added products. Zhang et al. [54] first pretreated corn stalks with water and ethanol under mild conditions to remove non-structural components. Then, the obtained pretreated corn stover was delignified with sodium chlorite. Their results show that selective removal of lignin can significantly promote the conversion of lignocellulose into fermentable sugars and platform chemicals (such as HMF). From the researches of Yan et al. [55] studied the process of different transition metal chlorides (such as FeCl3, RuCl3, VCl3, TiCl3, MoCl3 and CrCl3) catalyzing the production of HMF from cellulose in a two-phase system. Among these transition metal chlorides, RuCl3 is the most effective catalyst because RuCl3 enhances the decrystallization and cleavage of C-O-C bonds in cellulose, promotes the dehydration of glucose into 5-HMF, and inhibits the formation of by-product lactic acid. In addition, in the NaCl-water/butanol two-phase system, the highest HMF yield reached 83.3%, and the selectivity reached 87.5%. In Tyagi et al. [56] work, the effect of modified activated carbon catalytic acid combined with ionic liquid on the formation of HMF from Catalpa, Indian Rosewood, Babool and Chinaberry was studied. It is worth mentioning that Cao et al. [57] used sulfonated biochar from forest waste wood to catalyze breadcrumbs to produce HMF, which was a new and sustainable HMF production method, and the highest HMF yield could reach 30.4%. In DES/MIBK two-phase pretreatment system, HMF as byproducts was generated in the preparation of furfural from lignocellulose with $AlCl_3$ as catalyst [58]. High efficiency production of HMF form lignocellulose was achieved by the combination of dilute acid/alkali assisted pretreatment and catalytic conversion [59]. Jing et al. [60] found that in-situ carbonic acid from CO_2 as co-catalyst can effective promotive the hydrolysis of cellulose with metal oxide as catalyst. Seidel et al. [61] shown that 2-naphthol can promote the autohydrolysis pretreatment of softwood. In addition, the production of HMF is directly related to the concentration of 2-naphthol (as carbocation scavenger) during the two-stage steam explosion pretreatment. When treated in the THF/water biphasic system using $NaHSO_4$ and $ZnSO_4$ as catalysts or in the acetone–water system using H_3PO_4 as catalyst, the mixed saccharide feedstock can produce HMF [62]. Oktaviani et al. [63] measured the effects of maleic acid concentration on the production of sugar and by-products in sugarcane waste, corncobs and sweet sorghum bagasse. The results showed that after pretreatment with maleic acid, HMF and furfural were present in all biomass hydrolysates. Li et al. [64] synthesized a series of new composite material according to the efficient hydrolysis performance of the carbon catalyst and the high stability of niobia catalyst. Nb/C-50 catalyst, one of these materials, showed excellent activity and recyclability. The types of catalysts, experimental conditions, substrate conversion rates, and HMF yields in the above methods are summarized in Table 1.

In summary, Corn stalks, potato stems, girasol, foxtail weed, wood, Catalpa, Indian Rosewood, Babool, Chinaberry, bread crumbs, starch, straw, wood chips and cellulose can all be converted into HMF. The current high conversion method is first pretreatment/hydrolysis, and then catalytic conversion. Among them, the two-phase pretreatment system is relatively effective. Catalysts include transition metal chlorides, electrolyte-modified activated carbon, sulfonated bio-carbon and Namibia/carbon composites and other new types of catalysts. The utilization of carbon dioxide and electrolyte in the catalytic system also provides new ideas for the green and sustainable production of HMF. The acid sites of the catalyst play an important role in the conversion of cellulose to HMF. However, long reaction times and high doses of catalyst are the main challenges for large-scale HMF production.

3. Effects of HMF on anaerobic fermentation

3.1. Effects of HMF on hydrogen production in fermentation

In the pretreatment process, the types and concentrations of inhibitors depend on the pretreatment conditions [65]. Phenolic and furan derivatives are the most destructive inhibitors [66]. Determining the inhibiting effect of HMF on biofuel production is an important issue to be concerned [33]. Cao et al. [31] used the isolated *Thermoanaerobacterium thermosaccharolyticum* W16 to study the effect of lignin-derived inhibitors on its growth and hydrogen production. The results showed that adding 0.5 g/L of HMF reduced the cell concentration by 30%, and 1.5 g/L of HMF could completely inhibit hydrogen production. Siqueira and Reginatto [67] reported that HMF have effect on fermentative H_2 production by a mixed flora and 2.0 g/L HMF could promote the inhibition ratio reached 79.40%; the maximum hydrogen production rate was only 19.50% of control when the concentration of HMF was 1.0 g/L. HMF had stronger effect on the adaptation time of microorganisms on dark fermentation hydrogen production. HMF will reduce the number and types of hydrogen-producing microorganisms in the early stage, resulting in a stronger influence on the adaptation time of microorganisms to produce hydrogen in dark fermentation [37]. Anburajan et al. [68] also stated that HMF can significantly change the community structure of microorganisms. In Guo et al. [32] study, *Clostridium butyricum* was decreased with the increase of HMF concentration. At the same time, the number of *Lactobacillus* sp. increased.

Interestingly, low concentrations of HMF contribute to hydrogen production in fermentation. This suggests that the biodegradation products of HMF can be used to produce hydrogen [37]. Anburajan et al. [68] reported that when HMF concentration was 0.60 g/L, no inhibition of H_2 was detected and gas production was maximal; However, once the HMF concentration in the reactor exceeds 0.60 g/L, the H_2 production performance would be gradually inhibited; The 5-HMF concentration exceeding 0.9 g/L not only inhibits the production of hydrogen, but also affects the structure of the biofilm and the population of microbial communities. Confusingly, another study found that 0.59 g/L HMF inhibited hydrogen production hydrogen production was only 50% of that of the control; In addition, at 1.0 g / LHMF, hydrogen yield is 0 (mol/mol sugar) [69]. The reason for this difference is that the fermentation substrate and sludge used in each experiment are different. The former uses galactose, while the latter uses glucose [68,69]. In addition, the mesh structure of the filter in the fixed bed reactor (FBR) enhances the ability to grow and retain the microbial community with high H_2 production, which reduces the reduction in hydrogen production [68]. However, in the study of used a pure culture of *Clostridium butyricum* DSM 10,702 to ferment mixed sugars for hydrogen production, it was pointed out that HMF had an inhibitory effect at all concentrations (0–2.0 g/L). They pointed out that the results of various HMF concentrations in this study are different from the results of mixed cultures because pure culture using *C. Butricum* DSM 10,702 is used for hydrogen production and there is no HMF-degrading strain [70]. Effects of different concentrations of HMF on hydrogen production in fermentation are shown in Table 2.

Therefore, it appears that HMF within the range of 0.6 – 2.0 g/L, can inhibit hydrogen production in fermentation to different degrees, and can affect the community structure of fermentation microorganisms. Although there are some studies on the inhibition of HMF on biological hydrogen production, the inhibition mechanism is not well understood. In addition, Hu et al. [32] have studied they studied the inhibitory mechanism of eight representative lignocellulose derivative inhibitors (formic acid, hydroxybenzoic acid, ferulic acid, p-coumaric acid, furfural, HMF, vanillin and syringaldehyde) on biohydrogen fermentation, and the synergistic effect of the inhibitor mixture was discussed. They found that ferulic acid and p-coumaric acid are stronger than other inhibitors, and the main function inhibitors in the mixture are vanillin and syringaldehyde. The growth of the mixture on the concentration of higher inhibitors is strong than the total amount of the individual inhibitor. It is found that the inhibitor mixture has a clear synergistic effect of growth and related to inhibitor concentration. In the study of Yao et al. [71], the toxicity of furfural and HMF was not as good as the phenol inhibitor, furfural and HMF, which were completely converted to the corresponding alcohol, and the transformation speed of furfural was

Table 2
Effects of different concentrations of HMF on methane production in fermentation.

Concentration of HMF (g/L)	Fermentation products	Inoculum	Effects of HMF on fermentation	Ref
2.0	Biohydrogen	*T. thermosaccharolyticum* MJ1	Relative biohydrogen production was 74.40%; relative maximum OD660 value was 91.80%.	[33]
1.8	Biohydrogen	Anaerobic granular sludge	Hydrogen production performance was around 50% of the control	[68]
1.5	Biohydrogen	*T. thermosaccharolyticum* W16	Hydrogen production was completely inhibited	[31]
1.0	Biohydrogen	Anaerobic granular sludge	Hydrogen production was reduced 79%	[67]
1.0	Biohydrogen	*T. thermosaccharolyticum* W16	Hydrogen production was decrease 50.2%	[31]
1.0	Biohydrogen	Seed sludge	Hydrogen production activity was completely stopped	[69]
1.0	Biohydrogen	Anaerobic granular sludge	Hydrogen production rate was only 19.50% of control.	[67]
0.60	Biohydrogen	*T. thermosaccharolyticum* W16	H_2 production rate was inhibited by 25%	[31]
0.59	Biohydrogen	Anaerobic granular sludge	H_2-producing mixed flora was inhibited by 50%	[69]
0.48	Biohydrogen	Anaerobic granular sludge	50% of the maximum H2 production rate	[67]
0.43–0.50	Biomethane	anaerobic sludge	No obvious negative effect;	[74]
0.4	Biomethane	inoculum was taken from the digesters.	No inhibitory effect on methanogenesis	[75]
0.8	Biomethane	inoculum was taken from the digesters.	Methane production and methane production rate were decreased	[75]
2.0	Biomethane	inoculum was taken from the digesters.	Methanogenic activity was completely inhibited the	[75]
3	Biomethane	Granular sludge	Methane production was delayed; HMF was finally degraded and converted to biogas.	[76]
4	Bioethanol	*S. cerevisiae* CBS 8066,	Protein content was slightly reduced and total carbohydrate was slightly increased	[82]
2	Bioethanol	*S. cerevisiae* CBS 8066,	No significant changes in biomass composition	[82]
2.0	Bioethanol	*Saccharomyces cerevisiae*	Lag phase was prolongated	[83]
3.78	Bioethanol	*Saccharomyces cerevisiae*	The activities of the alcohol dehydrogenase were clearly decreased	[81]
5.04	Bioethanol	*Saccharomyces cerevisiae*	Translation was repressed and non-translated mRNAs were increased	[85]
8.82	Bioethanol	*Saccharomyces cerevisiae*	The attenuation of bulk translation activity and the assembly of cytoplasmic mRNP granules	[84]

faster than HMF. Finally, Kumar et al. [69] found that the inhibitory effect of HMF and levulinic acid is stronger than formic acid.

3.2. Effects of HMF on methane production in fermentation

Phuttaro et al. [72] found that Napier grass produced a certain amount of HMF after hydrothermal pretreatment, and HMF significantly inhibited anaerobic methanogenesis. In addition, the presence of HMF was also observed in the acid pretreated sugarcane bagasse and wheat straw hydrolysate, and the production of methane by anaerobic fermentation was inhibited [73].

Throughout the anaerobic digestion process of elephant grass hydrolysate, which contained HMF (0.43–0.50 g/L), the outlet effluent contained no HMF. In addition, the existence of HMF had no obvious negative effect on anaerobic digestion. This observation indicated that the microorganisms in the anaerobic sludge can use HMF as carbon source for biodegradation [74]. Ghasimi et al. [75] investigated the effects of several typical intermediates of lignocellulosic biomass on methanogenesis. The results showed that 0.4 g/L HMF had no effect; 0.8 g/L HMF had a moderate inhibitory effect, which greatly reduced the rate of methane production and yield; 2.0 g/L HMF had the maximum inhibitory effect, which completely inhibited the methanogenic activity. Interestingly, Park et al. [76] found that HMF delayed methane yield levels above 3 g/L. However, by increasing the concentration of cell biomass, the inhibitor is prevented, and the HMF is finally degraded and converted into biogas during anaerobic digestion of antithane biological ethanol residues. Barakat et al. [77] found similar results that HMF decreased the digestion rate but increased final methane production. Effects of different concentrations of HMF on methane production in fermentation are shown in Table 2.

In summary, it appears that when higher HMF concentration has negative effects on fermentation, it is likely to lead to lower anaerobic digestion rate, longer fermentation time, and less methane yield. On the contrary, when HMF concentration is low, anaerobic sludge is likely to use it as carbon source for utilization and conversion, which will eventually increase methane production, although it will cause fermentation delay. No research on the effect of HMF on the use of pure-bred microorganisms to produce methane has been found so far. One strategy might be to start each section with studies using pure cultures then move into the more complex communities of anaerobic digesters.

3.3. Effects of HMF on ethanol production and microbial growth

Ethanol production by biomass fermentation mainly uses the degradation and stabilization effect of yeast on organic matter, so as to convert biomass waste into energy substances that we can use. There are many studies on the effects of various toxic inhibitors produced by lignocellulose pretreatment on the growth, metabolism and fermentation of yeast. Studies have shown that these inhibitors can inhibit the normal growth and fermentation activity of yeast bacteria by interfering with cell membrane function, blocking the synthesis of important enzymes in the cell, and affecting the transcription of DNA [78-80].

Taherzadeh et al. [82] used glucose as a source of carbon and energy to cultivate *Saccharomyces cerevisiae* CBS 8066 in batches, and compared the effects of HMF and furan. The results showed that high concentration of HMF (4 g/L) has physiological effects on *Saccharomyces cerevisiae* CBS 8066, for example, reducing evolution rate of CO_2, reducing protein content, and increasing total carbohydrate content. However, a lower concentration of HMF (2 g/L) did not have a significant effect on biomass composition. Sanchez and Bautista [83] pointed out that HMF only prolonged the lag phase since HMF may be an intermediate product that is transformed by the yeast itself during the fermentation process. However, Iwaki et al. [84] and Ishida et al. [85] all pointed out that furan and HMF as stressors inhibit the growth and fermentation of yeast. Elevation of the nontranslating mRNA levels of Saccharomyces cerevisiae treated with furfural or HMF increased, which induced the formation of cytoplasmic mRNP particles and was accompanied by translational inhibition. Vanillin, furfural and HMF at a concentration of 7–10 mM did not strongly inhibit translation activity, but their combined stress severely inhibited translation [85].

4. Strategies to reduce the impact of HMF

There are four different ideas to reduce the inhibitory effect of HMF on biomass anaerobic fermentation: (1) avoid the formation of HMF in the process of biomass hydrolysis; (2) detoxify hydrolyzed products before fermentation; (3) screen and breed HMF resistant microbial species, and (4) convert HMF into products without inhibiting anaerobic fermentation. The key to detoxification is to separate inhibitors from hydrolysates without losing large amounts of fermentable materials [86]. Methods for detoxification of biomass hydrolysates have involved various directions including physical, chemical, and biological methods [87-89]. The main advantages and disadvantages of these techniques to reduce the impact of HMF are summarized in Table 3.

4.1. *Choosing the appropriate pretreatment to avoid HMF generation.*

4.1.1. *Oxidation pretreatment*

Oxidation pretreatment (Fig. 2) is mainly used to treat lignocellulose by oxidants with oxidation property. Furthermore, the most important feature of this pretreatment is that it does not produce inhibitory compounds and toxic substances to affect the subsequent hydrolysis and fermentation [90].

Ozone is a strong oxidizing agent and readily available for use. The reaction of ozone with lignin takes precedence over that with carbohydrates due to the high selectivity of ozone. In this way, it will be beneficial to reduce the consumption of carbohydrates, increase economic benefits. For decades, Ozonolysis has been used as an effective technique for different types of biomass to promote its deconstruction and delignification. Andersen et al. [91] indicated that ozonolysis pretreatment is able to improve the enzymatic saccharification of eucalyptus sawdust. However, taking into account of factors such as high cost and low efficiency in the process of using ozone, pretreatment schemes that combine ozone with other approaches for further effectively utilize biomass to produce energy substances have been reported [92]. Minmunin et al. [93] stated that Ozone treatment can be used with alkali solution pretreatment to enhance the efficiency of lignin elimination. In other study, the hydrolyzate obtained by pretreating the straw with NaOH and ozone successively had a high enzymatic efficiency [94]. Moreover, the combined pretreatment of ozone and ammonia can significantly increase the production of biomethane. This treatment can help dairy manure fiber and rice straw achieve better hydrolysis at low temperatures and low pressures compared to soaking in aqueous ammonia or ozonation alone [95].

4.1.2. *AFEX pretreatment*

Ammonia fiber explosion (AFEX) is a new technology that combines steam explosion with alkali treatment. When the pressure is swiftly released, ammonia will explode instantly, causing the expansion and physical destruction of biomass structure, and reducing the crystallization of cellulose and lignin (Fig. 3). This technique allows the biomass to be reacted in liquid anhydrous ammonia at elevated temperatures (90–100° C) and high pressure (1–5.2 MPa) for a period of time (30–60 min). Under such conditions, ammonia will explode instantly, causing the expansion and physical destruction of biomass structure, and reducing the crystallization of cellulose and lignin [96]. AFEX pretreatment produces almost no inhibitory compounds because only a small part of the raw material solids is dissolved and does not lead to the production of hemicellulose and lignin degradation products. Moreover, the hydrolyzed product can be used directly without further treatment, and the ammonia salt residue can be used as a microbial nutrient [97].

As an effective bagasse pretreatment method, AFEX pretreatment can not only improve enzymatic performance but also increase metabolizable energy content [98]. In addition, compared with steam explosion, AFEX pretreatment can endow sugarcane residues with higher fermentable sugar recovery and fermentability of enzymatic hydrolysates [99]. In addition, the sugar conversion rate of AFEX pretreated agave residue during the enzymatic hydrolysis process is about 85%, and the metabolism rate of ethanol exceeds 90% during the fermentation process without washing or adding any nutrients [100].

Table 3
Major advantages and disadvantages of methods to reduce the effect of HMF on fermentation.

Methods		Advantage	Disadvantages	
pretreatment	Oxidation pretreatment	Easy to use; High selectivity; Environmental.	High cost; Not economically feasible;Need a lot of ozone.	[90] [91]
	AFEX pretreatment	Environmental. The hydrolyzed product can be used directly; the ammonia salt residue can be used as microbial nutrition.	High cost; high volatility; Hazardous to the environment.	[96] [97] [98] [99]
	CO_2 explosion pretreatment	Non-toxic; Non-flammable; Easy to recycle after extraction; Low cost.	The pretreatment still needs to be improved.	[101]
	Microwave irradiation	Fast heat transfer; Short reaction time; Simple operation; High efficiency.	High cost;	[102] [103]
	Gamma ray radiation	Enhance the enzymatic hydrolysis of lignocellulosic biomass.	High cost;	[104] [105]
Removal and adsorption treatment.	Electrocoagulation technology	High efficiency and energy saving; High degree of automation; No secondary pollution.	High cost;	[107] [108]
	Flocculation	No loss of fermentable sugar.	poor cycle performance and complex recovery methods;	[109] [110]
	Adsorption	Reduce the loss of reducing sugars.	High cost.	[111] [116]
	Electrodialysis	High removal efficiency.	Easy to produce precipitation.	[118] [119] [122]
	Ion exchange resin	No loss of fermentable sugar; Good regeneration performance; low cost.	Low selectivity. High cost.	[24] [123]
Biological treatment	Selection of microorganism	Environment friendly; Selective degradation of ligninand hemicelluloses.	Very long pretreatment time (several weeks) due to slow yield	[126] [127] [132] [133] [134] [135] [136] [137] [138]
	Genetic and metabolic engineering	Environment friendly.	High cost. High difficulty	[140] [141] [143]

4.1.3. *CO_2 explosion pretreatment*

CO_2 explosion pretreatment refers to the rapid release of carbon dioxide in high pressure environment to destroy the crystal structure of the biomass, and then the weak acid formed by CO_2 further hydrolyzes the biomass residue in the reactor. This pretreatment technology costs more than steam explosions, but less than AFEX, and has good economic

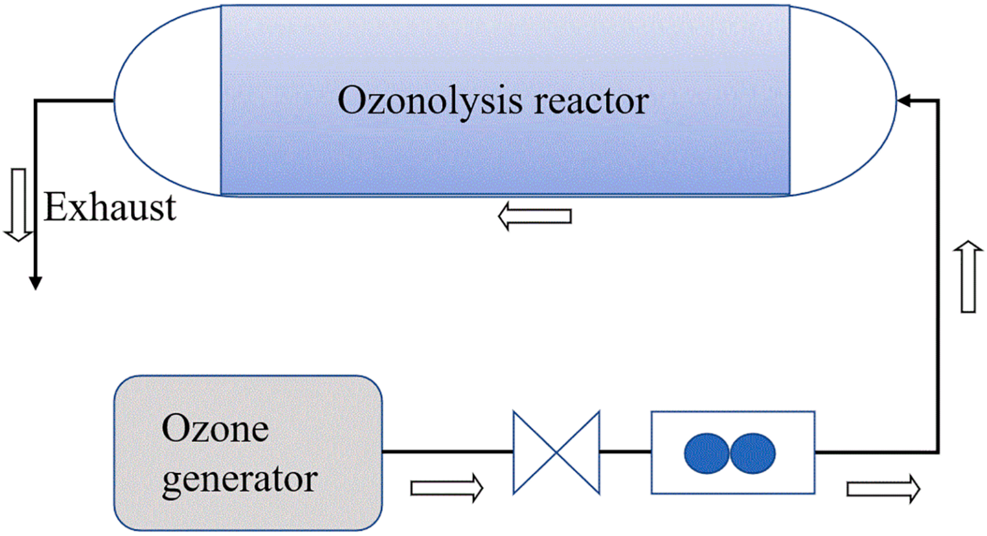

Fig. 2. Schematic diagram of oxidation pretreatment.

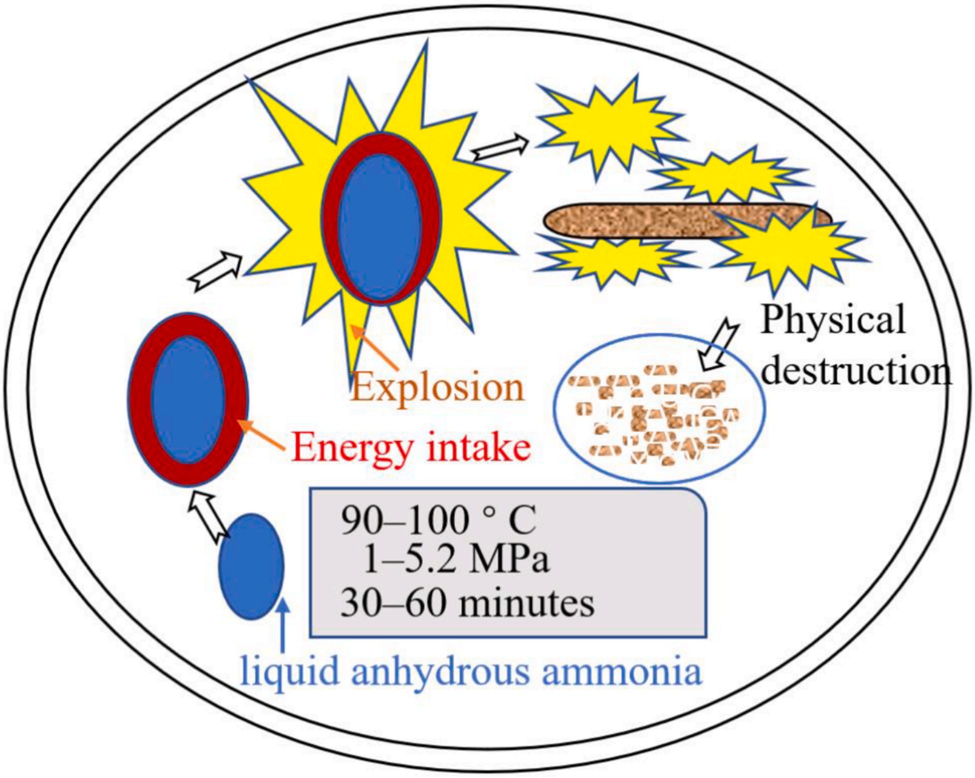

Fig. 3. Schematic diagram of ammonia fiber explosion treatment.

benefits in the process of ethanol fermentation. In addition, it has an important feature that no inhibitors are produced during the subsequent fermentation [101].

4.1.4. *Emerging technologies for pretreatment*

Microwave irradiation is not only a pretreatment method for biomass conversion into biofuel, but also a pretreatment method for biomass thermo-chemical pyrolysis [89]. Microwave pyrolysis has many advantages compared to conventional pyrolysis. First, the yield of gas products including hydrogen and methane will increase, which will increase economic benefits. Second, the addition of a suitable catalyst can increase the heating performance and change the selectivity to microwave pyrolysis products [102]. Reports show that in the study of the conversion of fructose into hydrogen coke, acidic seawater can promote the conversion of HMF under microwave heating conditions [103].

Gamma ray radiation has been demonstrated as a promising pretreatment technology of lignocellulosics. Ionizing radiation can easily penetrate the lignocellulosic structure, resulting in the modification of the lignin and destruction of the crystalline region of the cellulose [104]. Liu et al. [105] demonstrated that irradiation pretreatment of lignocellulose can reduce the particle size distribution and reduce the shear rate of the material. Their research results show that after irradiated pretreatment, the grinding of irradiated biomass requires only 1/3–1/4 of the energy consumption, compared with untreated biomass, and can achieve a finer particle size distributed. Specifically, the irradiated biomass is ground for 1 min, and the particle size distribution of less than 180 μm is 37–56%.

In addition, there are some emerging pretreatment techniques that are considered to have good application prospects in the utilization of lignincellulosic biomass. For example, high pressure hydrolysis, Electron beam irradiation, pulsed-electric field, ultrasound technologies and high-pressure homogenization. However, Hassan et al. [89] reported that the commercial application of these new technologies needs further feasibility study considering the complexity of bio-utilized process, the inter-dependencies of pretreatment processes and the economic benefits associated with the finished product market. In the latest research of Maitra and Singh [106], they found that a new method combining low-temperature hydrothermal pretreatment and low-temperature grinding can reduce inhibitor output and increase sugar recovery.

4.2. Using Non-biological methods to remove HMF from the hydrolysate.

Electrocoagulation technology has been widely used in the treatment of various wastewaters because it has excellent performance in the removal of some tough pollutants. It has many advantages, including high efficiency and energy saving, simple operation, high degree of automation, no secondary pollution, and relatively small and stable sludge generation. [107]. Recently, Jeong et al. [108] applied this technique to the removal of biological fermentation inhibitors in hydrolysates. The results show that the vast majority of HMF and furan can be effectively removed with little loss of sugars. Moreover, the experiment has the characteristics of simple operation, convenient conditions, short reaction time, and remarkable removal effect. Therefore, electrocoagulation technology is a good prospect for removing HMF from anaerobic feedstock.

Flocculation is a technology to improve solid–liquid separation and has the potential to recycle flocculant. An important feature of this technique is the ability to remove inhibitors while protecting the fermentable sugars from loss. Polyethylenimine (PEI) can be used in flocculation technology to effectively remove HMF. However, its cycle performance is poor and the recycling method is complicated. How to effectively reuse PEI in a complex environment to maximize its benefits is a challenge that is worth of studying. However, the biggest drawback of this technique is that additional steps are required to remove the polymer and adsorbate [109,110].

Adsorption is a simple and effective physical detoxification method for removing low concentration hydrophobic chemicals in water. Among the adsorbents, activated carbon has attracted much attention because of its strong adsorption capacity [111]. The effectiveness of activated carbon in removing inhibitors from hydrolysates has been demonstrated in other studies [112]. By optimizing the detoxification method of activated carbon, high efficiency of inhibitor removal was achieved under the condition of low reducing sugar loss. However, the high cost of producing activated carbon has hindered its full industrial application [113]. Since the production cost of pyrochar is less than one tenth of that of activated carbon, pyrochar produced from bioenergy residues is a more promising low-cost adsorbent [114]. Monlau et al. [115] studied the feasibility of detoxification of HMF in lignocellulosic hydrolysate using pyrochar. The results showed that pyrochar had a good detoxification effect on lignocellulosic hydrolysate and did not lead to loss of soluble sugars. In this process, the concentration of HMF can be increased to about 9 times the feed concentration by desorption experiments [116]. In research conducted by Chen et al [117], results show that under the best copolymerization conditions, the adsorbent HMF selectivity coefficient is 21.2.

Electrodialysis is an electrochemical process that uses electrical potential to drive the separation of cations and anions in solution. Recently, electrodialysis has been considered for the removal of fermentation inhibitors [118,119]. Unexpectedly, the ion exchange membrane can adsorb non-ionic fermentation inhibitors such as HMF while removing weak acid [120]. Similar results have been reported that electrodialysis was able to effectively remove 100% acetic acid and most HMF, furfural and phenolic compounds through the absorption by resin [121]. Trinh et al. [122] used a comprehensive detoxification process combining electrodialysis with adsorption to remove fermentation inhibitors such as acetic acid and HMF in the hydrolysate. Therefore, we can conclude that electrodialysis and adsorption can effectively reduce the effects of fermentation inhibitors such as HMF and improve fermentation performance.

Ion exchange resin treatment is a very promising method for removing HMF from acidic hydrolysates. Compared with activated carbon and adsorption resin, ion exchange resin overcomes the problems of difficulty in regeneration and high cost, and is a more common and effective method for separating valuable compounds from hydrolyzed products [24]. Kumar et al. [123] demonstrated that resin treatment efficiently removed HMF (50%) with no significant loss of sugars.

Liao et al. [124] designed a composite material with an active interface of nanoparticles and wrapped in a metal–organic framework that can effectively oxidize HMF to 2,5-furandicarboxylic acid (FDCA) under appropriate conditions, with a total conversion rate of 95%.

High-energy atmospheric cold plasma (ACP) is mainly used for semiconductors, food processing, medical sterilization and waste degradation. Lin et al. [125] used atmospheric cold plasma (ACP) to degrade the toxic substances in the sulfuric acid hydrolyzed bagasse. Studies have shown that ACP can remove 81% of HMF at 200 W power for 25 min.

4.3. Biological treatment to remove HMF from the hydrolysate.

4.3.1. Treatments with a variety of highly tolerant microorganisms

Some findings indicate that microbes are constantly evolving in a toxic environment, developing their ability to degrade HMF and achieving high tolerance to HMF [126]. These findings have greatly helped in the use of microorganisms to degrade HMF. Subsequently, the metabolic pathways and degradation mechanisms of HMF in some microorganisms have also been reported [127].

Biocatalytic oxidation is a promising addition to chemical methods. It has the advantages of environmentally friendly, good selectivity, high reaction efficiency and mild reaction conditions [128]. Zhang et al. [129] found that *Comamonas testosteroni* SC1588 is not only highly tolerant to HMF but also highly selective for formyl groups. This strain can significantly increase its resistance to environmental stress when exposed to the toxic stimulation of HMF [129]. This strain has broad application prospects in the detoxification of fermentation inhibitors because it has high tolerance and detoxification ability to HMF [130,131].

In another study, a complete biological transformation of HMF was achieved by *Acinetobacter oleivorans* S27. The tolerance concentration of this strain to HMF was up to 3000 mg/L [132].

Gluconobacter oxydans has a wide range of applications in the processes of incomplete oxidation of alcohols and sugars [133]. It has been reported that under pH-controlled conditions, a certain amount of HMF can be completely converted into 5-Hydroxymethyl-2-furan carboxylic acid (HMFCA) by selective oxidation of resting cells of *Gluconobacter oxydans* DSM 50,049 within 6 h [134]. Another study found that the *S. stipitis* KCTC 7228 was able to convert HMF into another less inhibitory compound(2,5-bis-hydroxymethylfuran) [135].

When using microorganisms to convert HMF in hydrolysate, it is better to convert HMF into carbon or energy sources [127,136]. A robust soil microorganism, *Pseudomonas putida* KT2440, can use HMF as carbon sources after fully loading the 12 kB HMF gene cluster by genetic recombination technology. This strain is superior to wild microorganisms in reducing lag time and increasing growth rate. The ability of the bacterium to adapt to the environment is improved, but its normal physiological function is inhibited by the high concentration of HMF toxicity, resulting in a decrease in growth rate and accumulation of transformed intermediates [136]. In addition, *Bordetella* sp. BTIITR almost completely removed HMF and furan in the hydrolysate in a 16 h incubation period. More interestingly, the bacterium had no significantly impact on the consumption of sugars before HMF is consumed to a lower concentration since the selective substrate priority of this strain towards HMF [137]. After that, the bacterium was applied to the study of removing HMF after being immobilized within chitosan beads. The results indicate that the immobilized cells are capable of degrading HMF in the hydrolysate over a greater temperature and pH ranges than free cells. Meanwhile, after the immobilization, the life cycle of the cells was prolonged, the tolerance concentration to HMF was improved, and the degradation efficiency was maintained [138]. The *Enterobacter* sp. FDS8 cells have also shown to be effective in the degradation of HMF in hydrolysates. The cells have good recyclability and almost no loss of sugars during the degradation process [131].

It is worth mentioning that the degradation rate of inhibitors can be accelerated in combination with biological treatment and other technical means. For example, He et al. [139] reported that the rate of biotransformation of HMF by *Amorphotheca resinae* ZN1 under aeration treatment was more than doubled, greatly reducing the detoxification time.

In summary, we can know that a number of microorganisms have high tolerance to HMF, including *Comamonas testosterone* SC1588, *Acinetobacter oleivorans* S27, *Gluconobacter oxydans* DSM 50049, S. *stipitis* KCTC 7228, *Pseudomonas putida* KT2440, *Bordetella* sp. BTIITR, and *Enterobacter* sp. FDS8, *Amorphotheca resinae* ZN1. The combination of various technologies provides a feasible way to improve the detoxification efficiency of inhibitors.

4.3.2. Treatments by utilizing the specificity of certain enzymes

In recent years, the selective catalytic oxidation of HMF by enzymes has attracted great interest. Because this environmentally friendly bioreactor system can help reduce the impact of pollution and has significant selectivity [140]. In a recent study, enzymes such as laccase and manganese peroxidase (MnP) have been proven to reduce HMF toxicity.

Laccase can perform a variety of biochemical reactions, which also makes it suitable for use in various fields. In addition, its oxidation selectivity and operational stability are maintained at very high levels in the reaction of aqueous solutions [141]. In the latest research, the recombinant CotA-TJ102, was obtained through heterologous expression and purification. After optimization of reaction parameters, the conversion ratio of HMF was nearly 100% in 12 h. The result indicated that the use of laccase to degrade and transform HMF is promising [142].

MnP is a heme perocidases, which is closely related to the ability of white rot fungi to degrade wood [143]. Hofrichter et al. [144] reported that MnP generates peroxy radicals during the oxidation of unsaturated fatty acids, which are highly oxidizing and can degrade some pollutants. Recently, Yee et al. [145] investigated the detoxification of recombinant manganese peroxidase to HMF. Although the degradation rate of HMF was fast in the early stages of the degradation treatment, HMF was not completely removed even after treatment for 100 h at a higher MnP concentration (200 U/L). Obviously, MnP treatment can slightly reduce the toxicity of HMF to microorganisms but does not significantly eliminate the inhibition of HMF.

5. Conclusions

In this review, we summarized the inhibitory effects of HMF on anaerobic fermentation and detoxification strategies. High concentration of HMF can disrupt the function and transformation of microbial macromolecules, impede the growth of microorganisms, change the community structure of microorganisms in anaerobic sludge, and inhibit the production of biofuels in anaerobic fermentation. However, high-tolerance microorganisms can convert HMF into other non-toxic substances, and even use it directly as a carbon source. At present, pretreatment and physicochemical methods can effectively reduce the inhibition effect of HMF. Genetically engineered microorganisms to convert HMF into other valuable products are the direction of future efforts.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (Grant No.: 51978178 and 51521006), the Department of Science and Technology of Guangdong Province of China (Contract No.: 2019A1515012044), Maoming Municipal Bureau of Science and Technology of Guangdong Province of China (Contract No.: 2018S0013), the International S&T Cooperation Program of China (Contract No.: 2015DFG92750), and the Research Funding of GDUPT (Grant No.: 2018rc63).

References

[1] M.-M. Titirici, M. Antonietti, N. Baccile, Hydrothermal carbon from biomass: a comparison of the local structure from poly- to monosaccharides and pentoses/hexoses, Green Chem. 10 (11) (2008) 1204, https://doi.org/10.1039/b807009a.

[2] H. Hu, Q. Zhou, X. Li, W. Lou, C. Du, Q. Teng, D.M. Zhang, H.Y. Liu, Y.Y. Zhong, C.P. Yang, Phytoremediation of anaerobically digested swine wastewater contaminated by oxytetracycline via Lemna aequinoctialis: Nutrient removal, growth characteristics and degradation pathways, Bioresour. Technol. 291 (2019) 121853, https://doi.org/10.1016/j.biortech.2019.121853.

[3] F. Monlau, C. Sambusiti, A. Barakat, M. Quemeneur, E. Trably, J.P. Steyer, H. Carrere, Do furanic and phenolic compounds of lignocellulosic and algae biomass hydrolyzate inhibit anaerobic mixed cultures? A comprehensive review, Biotechnol. Adv. 32 (2014) 934–951, https://doi.org/10.1016/j.biotechadv.2014.04.007.

[4] A. Effendi, H. Gerhauser, A.V. Bridgwater, Production of renewable phenolic resins by thermochemical conversion of biomass: A review, Renew. Sustain. Energy Rev. 12 (2008) 2092–2116, https://doi.org/10.1016/j.rser.2007.04.008.

[5] I.V. Saradhi, G.G. Pandit, V.D. Puranik, Energy supply. demand and environmental analysis–acase study of Indian energy scenario, Int. J. Environ. Sci. Eng. 3 (2009) 115–120, https://doi.org/10.1002/mnfr.201500469.

[6] S.J. Ai, H.Y. Liu, M.J. Wu, G.M. Zeng, C.P. Yang, Roles of acid-producing bacteria in anaerobic digestion of waste activated sludge, Front. Environ. Sci. Eng. 12 (6) (2018), https://doi.org/10.1007/s11783-018-1050-y.

[7] Z.F. Han, J. Dong, Z.Q. Shen, R. Mou, Y.X. Zhou, X.M. Chen, X.Y. Fu, C.P. Yang, Nitrogen removal of anaerobically digested swine wastewater by pilot-scale tidal flow constructed wetland based on in-situ biological regeneration of zeolite, Chemosphere 217 (2019) 364–373, https://doi.org/10.1016/j.chemosphere.2018.11.036.

[8] H. Hu, X. Li, S.H. Wu, C.P. Yang, Sustainable livestock wastewater treatment via phytoremediation: Current status and future perspectives, Bioresour. Technol. 315 (2020) 123809, https://doi.org/10.1016/j.biortech.2020.123809.

[9] X. Li, W.L. Yang, H.J. He, S.H. Wu, Q. Zhou, C.P. Yang, G.M. Zeng, L. Luo, W. Lou, Responses of microalgae Coelastrella sp to stress of cupric ions in treatment of anaerobically digested swine wastewater, Bioresour. Technol. 251 (2018) 274–279.

[10] Q. Zhou, X. Li, Y. Lin, C.P. Yang, W.C. Tang, S.H. Wu, D.H. Li, W. Lou, Effects of copper ions on removal of nutrients from swine wastewater and on release of dissolved organic matter in duckweed systems, Water Res. 158 (2019) 171–181, https://doi.org/10.1016/j.watres.2019.04.036.

[11] Q. Zhou, X. Li, S.H. Wu, Y.Y. Zhong, C.P. Yang, 2021 Enhanced strategies for antibiotics removal from swine wastewater in anaerobic digestion, Trends Biotechnol. 39 (1) (2021) 8–11, https://doi.org/10.1016/j.tibtech.2020.07.002.

[12] Y. Chen, J.J. Cheng, K.S. Creamer, Inhibition of anaerobic digestion process: A review, Bioresour. Technol. 99 (2008) 4044–4064, https://doi.org/10.1016/j.biortech.2007.01.057.

[13] J.Y. Guo, C.P. Yang, G.M. Zeng, Treatment of swine wastewater using chemically modified zeolite and bioflocculant from activated sludge, Bioresour. Technol. 143 (2013) 289–297, https://doi.org/10.1016/j.biortech.2013.06.003.

[14] X. Li, S.H. Wu, C.P. Yang, G.M. Zeng, Microalgal and duckweed based constructed wetlands for swine wastewater treatment: A review, Bioresour. Technol. 318 (2020), 123858, https://doi.org/10.1016/j.biortech.2020.123858.

[15] X. Li, C.P. Yang, G.M. Zeng, S.H. Wu, Y. Lin, Q. Zhou, W. Lou, C. Du, L.J. Nie, Y. Y. Zhong, Nutrient removal from swine wastewater with growing microalgae at various zinc concentrations, Algal Res. 46 (2020), 101804, https://doi.org/10.1016/j.algal.2020.101804.

[16] L. Luo, H.J. He, C.P. Yang, S. Wen, G.M. Zeng, M.J. Wu, Z.L. Zhou, W. Lou, Nutrient removal and lipid production by *Coelastrella sp.* in anaerobically and aerobically treated swine wastewater, Bioresour. Technol. 216 (2016) 135–141, https://doi.org/10.1016/j.biortech.2016.05.059.

[17] S. Wen, H.Y. Liu, H.J. He, L. Luo, X. Li, G.M. Zeng, Z.L. Zhou, W. Lou, C.P. Yang, Treatment of anaerobically digested swine wastewater by Rhodobacter blasticus and *Rhodobacter capsulatus*, Bioresour. Technol. 222 (2016) 33–38, https://doi.org/10.1016/j.biortech.2016.09.102.

[18] S. Behera, R. Arora, N. Nandhagopal, S. Kumar, Importance of chemical pretreatment for bioconversion of lignocellulosic biomass, Renew. Sustain. Energy Rev. 36 (2014) 91–106, https://doi.org/10.1016/j.rser.2014.04.047.

[19] G. Brodeur, E. Yau, K. Badal, J. Collier, K.B. Ramachandran, S. Ramakrishnan, Chemical and physicochemical pretreatment of lignocellulosic biomass: A review, Enz. Res. 2011 (2011), 787532, https://doi.org/10.4061/2011/787532.

[20] M.J. Wu, H.Y. Liu, J.Y. Guo, C.P. Yang, Enhanced enzymatic hydrolysis of wheat straw by two-step pretreatment combining alkalization and adsorption, Appl. Microbiol. Biotechnol. 102 (2018) 9831–9842, https://doi.org/10.1007/s00253-018-9335-4.

[21] V.B. Agbor, N. Cicek, R. Sparling, A. Berlin, D.B. Levin, Biomass pretreatment: Fundamentals toward application, Biotechnol. Adv. 29 (2011) 675–685, https://doi.org/10.1016/j.biotechadv.2011.05.005.

[22] S.H. Wu, Y. Lin, C.P. Yang, C. Du, Q. Teng, Y. Ma, D.M. Zhang, L.J. Nie, Y. Y. Zhong, Enhanced activation of peroxymonosulfte by $LaFeO_3$ perovskite supported on Al_2O_3 for degradation of organic pollutants, Chemosphere 237 (2019), 124478, https://doi.org/10.1016/j.chemosphere.2019.124478.

[23] A.T. Hendriks, G. Zeeman, Pretreatments to enhance the digestibility of lignocellulosic biomass, Bioresour. Technol. 100 (2009) 10–18, https://doi.org/10.1016/j.biortech.2008.05.027.

[24] K.F. Chen, S.L. Hao, H. Lyu, G. Luo, S.C. Zhang, J.M. Chen, Ion exchange separation for recovery of monosaccharides, organic acids and phenolic compounds from hydrolysates of lignocellulosic biomass, Sepa. Purif. Technol. 172 (2017) 100–106, https://doi.org/10.1016/j.seppur.2016.08.004.

[25] S. Shobana, G. Kumar, P. Bakonyi, G.D. Saratale, A.H. Al-Muhtaseb, N. Nemestóthy, K. Bélafi-Bakó, A. Xia, J.S. Chang, A review on the biomass pretreatment and inhibitor removal methods as key-steps towards efficient macroalgae-based biohydrogen production, Bioresour. Technol. 244 (2017) 1341–1348, https://doi.org/10.1016/j.biortech.2017.05.172.

[26] D. Steinbach, A. Kruse, J. Sauer, Pretreatment technologies of lignocellulosic biomass in water in view of furfural and 5-hydroxymethylfurfural production- A review, Biomass Convers. Biorefinery 7 (2017) 247–274, https://doi.org/10.1007/s13399-017-0243-0.

[27] M. Du, A.M. Agrawal, S. Chakraborty, S.J. Garibay, R. Limvorapitux, B. Choi, S. T. Madrahimov, S.T. Nguyen, Matching the activity of homogeneous sulfonic acids: The fructose-to-HMF conversion catalyzed by hierarchically porous sulfonic-scid-functionalized porous organic polymer (POP) catalysts, ACS Sustain. Chem. Eng. 7 (2019) 8126–8135, https://doi.org/10.1021/acssuschemeng.8b05720.

[28] F. Monlau, A. Barakat, J.P. Steyer, H. Carrere, Comparison of seven types of thermo-chemical pre-treatments on the structural features and anaerobic digestion of sunflower stalks, Bioresour. Technol. 120 (2012) 241–247, https://doi.org/10.1016/j.biortech.2012.06.040.

[29] I.K.M. Yu, D.C.W. Tsang, Conversion of biomass to hydroxymethylfurfural: A review of catalytic systems and underlying mechanisms, Bioresour. Technol. 238 (2017) 716–732, https://doi.org/10.1016/j.biortech.2017.04.026.

[30] X.L. Tong, Y. Ma, Y.D. Li, Biomass into chemicals: Conversion of sugars to furan derivatives by catalytic processes, Appl. Catal. A 385 (1–2) (2010) 1–13, https://doi.org/10.1016/j.apcata.2010.06.049.

[31] G.L. Cao, N.Q. Ren, A.J. Wang, W.Q. Guo, J.F. Xu, B.F. Liu, Effect of lignocellulose-derived inhibitors on growth and hydrogen production by *Thermoanaerobacterium thermosaccharolyticum W16*, Int. J. of Hydrog. Energy 35 (2010) 13475–13480, https://doi.org/10.1016/j.ijhydene.2009.11.127.

[32] L.D. Giraldeli, B.C. Fonseca, V. Reginatto, Mixtures of 5-hydroxymethylfurfural, levulinic acid, and formic acid have different impact on H_2-producing *Clostridium strains*, Int. J. Hydrog. Energy 43 (2018) 22159–22169, https://doi.org/10.1016/j.ijhydene.2018.10.051.

[33] B.B. Hu, J.L. Wang, Y.T. Wang, M.J. Zhu, Specify the individual and synergistic effects of lignocellulose-derived inhibitors on biohydrogen production and inhibitory mechanism research, Renew. Energy 140 (2019) 397–406, https://doi.org/10.1016/j.renene.2019.03.050.

[34] M. Dashtban, A. Gilbert, P. Fatehi, Recent advancements in the production of hydroxymethylfurfural, RSC Adv. 4 (4) (2014) 2037–2050, https://doi.org/10.1039/c3ra45396k.

[35] M.A. Kougioumtzis, A. Marianou, K. Atsonios, C. Michailof, N. Nikolopoulos, N. Koukouzas, K. Triantafyllidis, A. Lappas, E. Kakaras, Production of 5-HMF from cellulosic biomass: Experimental results and integrated process simulation, Waste Biomass Valorization 9 (2018) 2433–2445, https://doi.org/10.1007/s12649-018-0267-0.

[36] R.L.K. Nilsson, M. Holmgren, B. Madavi, R.T. Nilsson, A. Sellstedt, Adaptability of Trametes versicolor to the lignocellulosic inhibitors furfural, HMF, phenol and levulinic acid during ethanol fermentation, Biomass Bioenerg. 90 (2016) 95–100, https://doi.org/10.1016/j.biombioe.2016.03.030.

[37] K.M. Muñoz-Páez, E.L. Alvarado-Michi, G. Buitrón, I. Valdez-Vazquez, Distinct effects of furfural, hydroxymethylfurfural and its mixtures on dark fermentation hydrogen production and microbial structure of a mixed culture, Int. J. Hydrog. Energy 44 (2019) 2289–2297, https://doi.org/10.1016/j.ijhydene.2018.04.139.

[38] M.J. Antal, W.S.L. Mok, G.N. Richards, Mechanism of formation of 5-(hydroxymethyl)-2-furaldehyde from d-fructose and sucrose, Carbohydr. Res. 199 (1990) 91–109, https://doi.org/10.1016/0008-6215(90)84096-D.

[39] Q. Wang, M.X. Fu, X.J. Li, R.F. Huang, R.E. Glaser, L.L. Zhao, Aluminum alkoxy-catalyzed biomass conversion of glucose to 5-hydroxymethylfurfural: Mechanistic study of the cooperative bifunctional catalysis, J. Comput. Chem. 40 (16) (2019) 1599–1608, https://doi.org/10.1002/jcc.25812.

[40] A. Rusanen, R. Lahti, K. Lappalainen, J. Kärkkäinen, T. Hu, H. Romar, U. Lassi, Catalytic conversion of glucose to 5-hydroxymethylfurfural over biomassbased activated carbon catalyst, Catal. Today 357 (2020) 94–101, https://doi.org/10.1016/j.cattod.2019.02.040.

[41] M. Zuo, W.L. Jia, Y.C. Feng, X.H. Zeng, X. Tang, Y. Sun, L. Lin, Effective selectivity conversion of glucose to furan chemicals in the aqueous deep eutectic solvent, Renew. Energ. 164 (2021) 23–33, https://doi.org/10.1016/j.renene.2020.09.019.

[42] W. Guo, H.J. Heeres, J. Yue, Continuous synthesis of 5-hydroxymethylfurfural from glucose using a combination of AlCl3 and HCl as catalyst in a biphasic slug flow capillary microreactor, Chem. Eng. J. 381 (2020) 122754, https://doi.org/10.1016/j.cej.2019.122754.

[43] G.T.T. Le, K. Arunaditya, J. Panichpol, T. Rodruangnon, S. Thongratkaew, K. Chaipojjana, K. Faungnawakij, T. Charinpanitkul, Sulfonated magnetic carbon nanoparticles from eucalyptus oil as a green and sustainable catalyst for converting fructose to 5-HMF, Catal. Commun. 149 (2021) 106229, https://doi.org/10.1016/j.catcom.2020.106229.

[44] Z. Tang, J. Su, One step conversion of glucose into 5-hydroxymethylfurfural (HMF) via a basic catalyst in mixed solvent systems of ionic iiquid-dimethyl sulfoxide, J. Oleo Sci. 68 (2019) 261–271, https://doi.org/10.5650/jos.ess18196.

[45] T.W. Zhang, W.Z. Li, H.S. Xin, L.L. Jin, Q.Y. Liu, Production of HMF from glucose using an Al^{3+}-promoted acidic phenol-formaldehyde resin catalyst, Catal. Commun. 124 (2019) 56–61, https://doi.org/10.1016/j.catcom.2019.03.001.

[46] A.A. Marianou, C.M. Michailof, A. Pineda, E.F. Iliopoulou, K.S. Triantafyllidis, A. A. Lappas, Effect of Lewis and Brønsted acidity on glucose conversion to 5-HMF and lactic acid in aqueous and organic media, Appl. Catal. A-Gen. 555 (2018) 75–87, https://doi.org/10.1016/j.apcata.2018.01.029.

[47] P. Körner, D. Jung, A. Kruse, The effect of different Brønsted acids on the hydrothermal conversion of fructose to HMF, Green Chem. 20 (2018) 2231–2241, https://doi.org/10.1039/c8gc00435h.

[48] J. Tacacima, S. Derenzo, J.G.R. Poco, Synthesis of HMF from fructose using Purolite® strong acid catalyst: Comparison between BTR and PBR reactor type for kinetics data acquisition, Molecular Catalysis 458 (2018) 180–188, https://doi.org/10.1016/j.mcat.2017.12.021.

[49] K.T.V. Rao, S. Souzanchi, Z.S. Yuan, M.B. Ray, C.B. Xu, Simple and green route for preparation of tin phosphate catalysts by solid-state grinding for dehydration of glucose to 5-hydroxymethylfurfural (HMF), RSC Adv. 7 (76) (2017) 48501–48511, https://doi.org/10.1039/C7RA10083C.

[50] F. Parveen, S. Upadhyayula, Efficient conversion of glucose to HMF using organocatalysts with dual acidic and basic functionalities - A mechanistic and experimental study, Fuel Process. Technol. 162 (2017) 30–36, https://doi.org/10.1016/j.fuproc.2017.03.021.

[51] L.X. Zhang, G.Y. Xi, Z. Chen, Z.Y. Qi, X.C. Wang, Enhanced formation of 5-HMF from glucose using a highly selective and stable SAPO-34 catalyst, Chem. Eng. J. 307 (2017) 877–883, https://doi.org/10.1016/j.cej.2016.09.003.

[52] S.T. Pham, M.B. Nguyen, G.H. Le, T.D. Nguyen, C.D. Pham, T.S. Le, T.A. Vu, Influence of Brønsted and Lewis acidity of the modified Al-MCM-41 solid acid on cellulose conversion and 5-hydroxylmethylfurfuran selectivity, Chemosphere 265 (2021), 129062, https://doi.org/10.1016/j.chemosphere.2020.129062.

[53] G.D. Jin, M. Yang, E. Shuang, J.L. Liu, S. Zhang, X.L. Zhang, K.C. Sheng, X. M. Zhang, Corn stover valorization by one-step formic acid fractionation and formylation for 5-hydroxymethylfurfural and high guaiacyl lignin production, Bioresour. Technol. 299 (2020), 122586, https://doi.org/10.1016/j.biortech.2019.122586.

[54] J. Zhang, Y.H. Wang, X.J. Du, Y.S. Qu, Selective removal of lignin to enhance the process of preparing fermentable sugars and platform chemicals from lignocellulosic biomass, Bioresour. Technol. 303 (2020), 122846, https://doi.org/10.1016/j.biortech.2020.122846.

[55] L.S. Yan, R.S. Ma, H.X. Wei, L.Z. Li, B. Li, Y.W. Xu, Ruthenium trichloride catalyzed conversion of cellulose into 5-hydroxymethylfurfural in biphasic system, Bioresour. Technol. 279 (2019) 84–91, https://doi.org/10.1016/j.biortech.2019.01.120.

[56] U. Tyagi, N. Anand, D. Kumar, Simultaneous pretreatment and hydrolysis of hardwood biomass species catalyzed by combination of modified activated carbon and ionic liquid in biphasic system, Bioresour. Technol. 289 (2019) 121675, https://doi.org/10.1016/j.biortech.2019.121675.

[57] L.C. Cao, I.K.M. Yu, S.S. Chen, D.C.W. Tsang, L. Wang, X.N. Xiong, S.C. Zhang, Y. S. Ok, E.E. Kwon, H. Song, C.S. Poon, Production of 5-hydroxymethylfurfural from starch-rich food waste catalyzed by sulfonated biochar, Bioresour. Technol. 252 (2018) 76–82, https://doi.org/10.1016/j.biortech.2017.12.098.

[58] Z.K. Wang, X.J. Shen, J.J. Chen, Y.Q. Jiang, Z.Y. Hu, X. Wang, L. Liu, Lignocellulose fractionation into furfural and glucose by $AlCl_3$-catalyzed DES/MIBK biphasic pretreatment, Int. J. Biol. Macromol. 117 (2018) 721–726, https://doi.org/10.1016/j.ijbiomac.2018.05.232.

[59] C.V. Nguyen, D. Lewis, W.H. Chen, H.W. Huang, Z.A. Alothman, Y. Yamauchi, K. C.W. Wu, Combined treatments for producing 5-hydroxymethylfurfural (HMF) from lignocellulosic biomass, Catal. Today 278 (2016) 344–349, https://doi.org/10.1016/j.cattod.2016.03.022.

[60] S.S. Jing, X.F. Cao, L.X. Zhong, X.W. Peng, R.C. Sun, J.C. Liu, Effectively enhancing conversion of cellulose to HMF by combining in-situ carbonic acid from CO_2 and metal oxides, Ind. Crop. Prod. 126 (2018) 151–157, https://doi.org/10.1016/j.indcrop.2018.10.028.

[61] C.M. Seidel, S. Brethauer, L. Gyenge, P.R. Rudolf von Rohr, M.H. Studer, Two-stage steam explosion pretreatment of softwood with 2-naphthol as carbocation scavenger, Biotechnol. Biofuels 12 (2019) 37, https://doi.org/10.1186/s13068-019-1373-3.

[62] P. Widsten, K. Murton, M. West, Production of 5-hydroxymethylfurfural and furfural from a mixed saccharide feedstock in biphasic solvent systems, Ind. Crop. Prod. 119 (2018) 237–242, https://doi.org/10.1016/j.indcrop.2018.04.032.

[63] M. Oktaviani, E. Hermiati, A. Thontowi, R.P.B. Laksana, L.N. Kholida, A. Andriani, W. YopiMangunwardoyo, Production of xylose, glucose, and other products from tropical lignocellulose biomass by using maleic acid pretreatment, IOP Conf. Ser. Earth Envir. Sci. 251 (2019), 012013, https://doi.org/10.1088/1755-1315/251/1/012013.

[64] X.C. Li, K.H. Peng, Q.N. Xia, X.H. Liu, Y.Q. Wang, Efficient conversion of cellulose into 5-hydroxymethylfurfural over niobia/carbon composites, Chem. Eng. J. 332 (2018) 528–536, https://doi.org/10.1016/j.cej.2017.06.105.

[65] L.J. Jonsson, C. Martin, Pretreatment of lignocellulose: Formation of inhibitory by-products and strategies for minimizing their effects, Bioresour. Technol. 199 (2016) 103–112, https://doi.org/10.1016/j.biortech.2015.10.009.

[66] A. Mudhoo, P.C. Torres-Mayanga, T. Forster-Carneiro, P. Sivagurunathan, G. Kumar, D. Komilis, A. Sanchez, A review of research trends in the enhancement of biomass-to-hydrogen conversion, Waste Manage. 79 (2018) 580–594, https://doi.org/10.1016/j.wasman.2018.08.028.

[67] M.R. Siqueira, V. Reginatto, Inhibition of fermentative H_2 production by hydrolysis byproducts of lignocellulosic substrates, Renew. Energy 80 (2015) 109–116, https://doi.org/10.1016/j.renene.2015.01.070.

[68] P. Anburajan, A. Pugazhendhi, J.H. Park, P. Sivagurunathan, G. Kumar, S.H. Kim, Effect of 5-hydroxymethylfurfural (5-HMF) on high-rate continuous biohydrogen production from galactose, Bioresour. Technol. 247 (2018) 1197–1200, https://doi.org/10.1016/j.biortech.2017.09.001.

[69] G. Kumar, H.C. Cheon, S.H. Kim, Effects of 5-hydromethylfurfural, levulinic acid and formic acid, pretreatment byproducts of biomass, on fermentative H_2 production from glucose and galactose, Int. J. Hydrogen Energy 39 (2014) 16885–16890, https://doi.org/10.1016/j.ijhydene.2014.08.063.

[70] D.H. Kim, J.J. Yoon, S.H. Kim, J.H. Park, Effect of conductive material for overcoming inhibitory conditions derived from red algae-based substrate on biohydrogen production, Fuel 285 (2021) 119059, https://doi.org/10.1016/j.fuel.2020.119059.

[71] D.F. Yao, S. Dong, P.X. Wang, T.H. Chen, J. Wang, Z.B. Yue, Y. Wang, Robustness of *Clostridium saccharoperbutylacetonicum* for acetone-butanol-ethanol production: Effects of lignocellulosic sugars and inhibitors, Fuel 208 (2017) 549–557, https://doi.org/10.1016/j.fuel.2017.07.004.

[72] C. Phuttaro, C. Sawatdeenarunat, K.C. Surendra, P. Boonsawang, S. Chaiprapat, S. K. Khanal, Anaerobic digestion of hydrothermally-pretreated lignocellulosic biomass: Influence of pretreatment temperatures, inhibitors and soluble organics on methane yield, Bioresour. Technol. 284 (2019) 128–138, https://doi.org/10.1016/j.biortech.2019.03.114.

[73] S. Bolado-Rodríguez, C. Toquero, J. Martín-Juárez, R. Travaini, P.A. García-Encina, Effect of thermal, acid, alkaline and alkaline-peroxide pretreatments on the biochemical methane potential and kinetics of the anaerobic digestion of wheat straw and sugarcane bagasse, Bioresour. Technol. 201 (2016) 182–190, https://doi.org/10.1016/j.biortech.2015.11.047.

[74] C. Huang, L. Xiong, H.J. Guo, H.L. Li, C. Wang, X.F. Chen, C. Zhao, X.D. Chen, Anaerobic digestion of elephant grass hydrolysate: Biogas production, substrate metabolism and outlet effluent treatment, Bioresour. Technol. 283 (2019) 191–197, https://doi.org/10.1016/j.biortech.2019.03.079.

[75] D.S.M. Ghasimi, K. Aboudi, M. de Kreuk, M.H. Zandvoort, J.B. van Lier, Impact of lignocellulosic-waste intermediates on hydrolysis and methanogenesis under thermophilic and mesophilic conditions, Chem. Eng. J. 295 (2016) 181–191, https://doi.org/10.1016/j.cej.2016.03.045.

[76] J.H. Park, J.J. Yoon, H.D. Park, D.J. Lim, S.H. Kim, Anaerobic digestibility of algal bioethanol residue, Bioresour. Technol. 113 (2012) 78–82, https://doi.org/10.1016/j.biortech.2011.12.123.

[77] A. Barakat, F. Monlau, J.P. Steyer, H. Carrere, Effect of lignin-derived and furan compounds found in lignocellulosic hydrolysates on biomethane production, Bioresour. Technol. 104 (2012) 90–99, https://doi.org/10.1016/j.biortech.2011.10.060.

[78] M.A. Franden, H.M. Pilath, A. Mohagheghi, P.T. Pienkos, M. Zhang, Inhibition of growth of zymomonas mobilis by model compounds found in lignocellulosic hydrolysates, Biotechnol. Biofuels 6 (2013) 99, https://doi.org/10.1186/1754-6834-6-99.

[79] M.X. He, B. Wu, Z.X. Shui, Q.C. Hu, W.G. Wang, F.R. Tan, X.Y. Tang, Q.L. Zhu, K. Pan, Q. Li, X.H. Su, Transcriptome profiling of Zymomonas mobilis under furfural stress, Appl. Microbiol. Biotechnol. 95 (2012) 189–199, https://doi.org/10.1007/s00253-012-4155-4.

[80] E.C. van der Pol, R.R. Bakker, P. Baets, G. Eggink, By-products resulting from lignocellulose pretreatment and their inhibitory effect on fermentations for (bio) chemicals and fuels, Appl. Microbiol. Biotechnol. 98 (2014) 9579–9593, https://doi.org/10.1007/s00253-014-6158-9.

[81] T. Modig, G. Liden, M.J. Taherzadeh, Inhibition effects of furfural on alcohol dehydrogenase, aldehyde dehydrogenase and pyruvate dehydrogenase, Biochem. J. 363 (2002) 769–776, https://doi.org/10.1042/0264-6021:3630769.

[82] M.J. Taherzadeh, L. Gustafsson, C. Niklasson, G. Liden, Physiological effects of 5-hydroxymethylfurfural on *Saccharomyces cerevisiae*, Appl. Microbiol. Biotechnol. 53 (2000) 701–708, https://doi.org/10.1007/s002530000328.

[83] B. Sanchez, J. Bautista, Effects of furfural and 5-hydroxymethylfurfural on the fermentation of *Saccharomyces cerevisiae* and biomass production from Candida guilliermondii, Enzyme Microb. Technol. 10 (1988) 315–318, https://doi.org/10.1016/0141-0229(88)90135-4.

[84] A. Iwaki, T. Kawai, Y. Yamamoto, S. Izawa, Biomass Conversion Inhibitors Furfural and 5-Hydroxymethylfurfural Induce Formation of Messenger RNP Granules and Attenuate Translation Activity in *Saccharomyces cerevisiae*, Appl. Environ. Microbiol. 79 (5) (2013) 1661–1667, https://doi.org/10.1128/AEM.02797-12.

[85] Y. Ishida, T.T.M. Nguyen, S. Izawa, The yeast ADH7 promoter enables gene expression under pronounced translation repression caused by the combined stress of vanillin, furfural, and 5-hydroxymethylfurfural, J. Biotechnol. 252 (2017) 65–72, https://doi.org/10.1016/j.jbiotec.2017.04.024.

[86] D. Cannella, P.V. Sveding, H. Jørgensen, PEI detoxification of pretreated spruce for high solids ethanol fermentation, Appl. Energy 132 (2014) 394–403, https://doi.org/10.1016/j.apenergy.2014.07.038.

[87] A. Cavka, L.J. Jonsson, Detoxification of lignocellulosic hydrolysates using sodium borohydride, Bioresour. Technol. 136 (2013) 368–376, https://doi.org/10.1016/j.biortech.2013.03.014.

[88] Y.H. Weng, H.J. Wei, T.Y. Tsai, T.H. Lin, T.Y. Wei, G.L. Guo, C.P. Huang, Separation of furans and carboxylic acids from sugars in dilute acid rice straw hydrolyzates by nanofiltration, Bioresour. Technol. 101 (2010) 4889–4894, https://doi.org/10.1016/j.biortech.2009.11.090.

[89] Y. Lin, S.H. Wu, C.P. Yang, M. Chen, X. Li, Preparation of size-controlled silver phosphate catalysts and their enhanced photocatalysis performance via synergetic effect with MWCNTs and PANI, Appl. Catal. B-Environ. 245 (2019) 71–86, https://doi.org/10.1016/j.apcatb.2018.12.048.

[90] S.S. Hassan, G.A. Williams, A.K. Jaiswal, Emerging technologies for the pretreatment of lignocellulosic biomass, Bioresour. Technol. 262 (2018) 310–318, https://doi.org/10.1016/j.biortech.2018.04.099.

[91] S.L.F. Andersen, R. Castoldi, J.A.A. Garcia, A. Bracht, R.A. Peralta, E.A. de Lima, C.V. Helm, R.D.P.M. Moreira, R.M. Peralta, Improving enzymatic saccharification of Eucalyptus grandis branches by ozone pretreatment, Wood Sci. Technol. 53 (2019) 49–69, https://doi.org/10.1007/s00226-018-1061-7.

[92] H. Ikeura, S. Hamasaki, M. Tamaki, Effects of ozone microbubble treatment on removal of residual pesticides and quality of persimmon leaves, Food Chem. 138 (2013) 366–371, https://doi.org/10.1016/j.foodchem.2012.09.139.

[93] J. Minmunin, P. Limpitipanich, A. Promwungkwa, Delignification of bana grass using sodium hydroxide and ozone, Waste Biomass Valorization 9 (2018) 2099–2105, https://doi.org/10.1007/s12649-017-0002-2.

[94] W.H. Wang, C.Y. Zhang, S.S. Tong, Z.Y. Cui, P. Liu, Enhanced enzymatic hydrolysis and structural features of corn stover by NaOH and ozone combined pretreatment, Molecules 23 (2018) 1300, https://doi.org/10.3390/molecules23061300.

[95] P. Ai, X.z. Zhang, C. Dinamarca, M. Elsayed, L. Yu, J. Xi, Z.l. Mei, Different effects of ozone and aqueous ammonia in a combined pretreatment method on rice straw and dairy manure fiber for enhancing biomethane production, Bioresour. Technol. 282 (2019) 275–284, https://doi.org/10.1016/j.biortech.2019.03.021.

[96] L. Laureano-Perez, F. Teymouri, H. Alizadeh, B.E. Dale, Understanding factors that limit enzymatic hydrolysis of biomass, Appl. Biochem. Biotechnol. 121 (2005) 1081–1099, https://doi.org/10.1007/978-1-59259-991-2_91.

[97] D. Kim, Physico-chemical conversion of lignocellulose: Inhibitor effects and detoxification strategies: A Mini Review, Molecules 23 (2018) 309, https://doi.org/10.3390/molecules23020309.

[98] T. Mokomele, L.D. da Costa Sousa, B. Bals, V. Balan, N. Goosen, B.E. Dale, J. F. Görgens, Using steam explosion or AFEXTM to produce animal feeds and biofuel feedstocks in a biorefinery based on sugarcane residues, Biofuels Bioprod. Biorefining 12 (2018) 978–996, https://doi.org/10.1002/bbb.1927.

[99] T. Mokomele, L.D. da Costa Sousa, V. Balan, E. van Rensburg, B.E. Dale, J. F. Gorgens, Ethanol production potential from AFEXTM and steam-exploded sugarcane residues for sugarcane biorefineries, Biotechnol. Biofuels 11 (2018) 127, https://doi.org/10.1186/s13068-018-1130-z.

[100] C.A. Flores-Gomez, E.M. Escamilla Silva, C. Zhong, B.E. Dale, L. da Costa Sousa, V. Balan, Conversion of lignocellulosic agave residues into liquid biofuels using an AFEXTM-based biorefinery, Biotechnol. Biofuels 11 (2018) 7, https://doi.org/10.1186/s13068-017-0995-6.

[101] K. Ohgren, R. Bura, J. Saddler, G. Zacchi, Effect of hemicellulose and lignin removal on enzymatic hydrolysis of steam pretreated corn stover, Bioresour. Technol. 98 (2007) 2503–2510, https://doi.org/10.1016/j.biortech.2006.09.003.

[102] Y.F. Huang, P.T. Chiueh, S.L. Lo, A review on microwave pyrolysis of lignocellulosic biomass, Sustain. Environ. Res. 26 (2016) 103–109, https://doi.org/10.1016/j.serj.2016.04.012.

[103] Y.C. Shao, W.J. Lu, D. Zhou, D.S. Shen, Y.Y. Long, The formation of 5-hydroxymethylfurfural and hydrochar during the valorization of biomass using a microwave hydrothermal method, Sci. Total Environ. 755 (2021), 142499, https://doi.org/10.1016/j.scitotenv.2020.142499.

[104] C.P Yang, Z.Q. Shem, G. Yu, J.L. Wang, Effect and aftereffect of γ radiation pretreatment on enzymatic hydrolysis of wheat straw, Bioresour. Technol. 99 (14) (2008) 6240–6245, https://doi.org/10.1016/j.biortech.2007.12.008.

[105] Y. Liu, L.J. Guo, L.Y. Wang, W. Zhan, H. Zhou, Irradiation pretreatment facilitates the achievement of high total sugars concentration from lignocellulose biomass, Bioresour. Technol. 232 (2017) 270–277, https://doi.org/10.1016/j.biortech.2017.01.061.

[106] S. Maitra, V. Singh, Balancing sugar recovery and inhibitor generation during energycane processing: Coupling cryogenic grinding with hydrothermal pretreatment at low temperatures, Bioresour. Technol. 321 (2021), 124424, https://doi.org/10.1016/j.biortech.2020.124424.

[107] D.T. Moussa, M.H. El-Naas, M. Nasser, M.J. Al-Marri, A comprehensive review of electrocoagulation for water treatment: Potentials and challenges, J. Environ. Manage. 186 (2017) 24–41, https://doi.org/10.1016/j.jenvman.2016.10.032.

[108] H. Jeong, J. Lee, Y.M. Ju, S.M. Lee, Using electro-coagulation treatment to remove phenolic compounds and furan derivatives in hydrolysates resulting from pilot-scale supercritical water hydrolysis of Mongolian oak, Renewable Energy 138 (2019) 971–979, https://doi.org/10.1016/j.renene.2019.01.115.

[109] B. Carter, P.C. Gilcrease, T.J. Menkhaus, Removal and recovery of furfural, 5-hydroxymethylfurfural, and acetic acid from aqueous solutions using a soluble polyelectrolyte, Biotechnol. Bioeng. 108 (2011) 2046–2052, https://doi.org/10.1002/bit.23153.

[110] F. Deng, G.M. Aita, Detoxification of dilute ammonia pretreated energy cane bagasse enzymatic hydrolysate by soluble polyelectrolyte flocculants, Ind. Crop. Prod. 112 (2018) 681–690, https://doi.org/10.1016/j.indcrop.2017.12.061.

[111] T. Sainio, I. Turku, J. Heinonen, Adsorptive removal of fermentation inhibitors from concentrated acid hydrolyzates of lignocellulosic biomass, Bioresour. Technol. 102 (2011) 6048–6057, https://doi.org/10.1016/j.biortech.2011.02.107.

[112] R.L. Kudahettige-Nilsson, J. Helmerius, R.T. Nilsson, M. Sjoblom, D.B. Hodge, U. Rova, Biobutanol production by *Clostridium acetobutylicum* using xylose recovered from birch Kraft black liquor, Bioresour. Technol. 176 (2015) 71–79, https://doi.org/10.1016/j.biortech.2014.11.012.

[113] C.H. Luo, F. Lü, L.M. Shao, P.J. He, Application of eco-compatible biochar in anaerobic digestion to relieve acid stress and promote the selective colonization of functional microbes, Water Res. 68 (2015) 710–718, https://doi.org/10.1016/j.watres.2014.10.052.

[114] Y.C. Li, J.G. Shao, X.H. Wang, H.P. Yang, Y.Q. Chen, Y. Deng, S.H. Zhang, H. P. Chen, Upgrading of bio-oil: removal of the fermentation inhibitor (Furfural) from the model compounds of bio-oil using pyrolytic char, Energy Fuels 27 (10) (2013) 5975–5981, https://doi.org/10.1021/ef401375q.

[115] F. Monlau, C. Sambusiti, N. Antoniou, A. Zabaniotou, A. Solhy, A. Barakat, Pyrochars from bioenergy residue as novel bio-adsorbents for lignocellulosic hydrolysate detoxification, Bioresour. Technol. 187 (2015) 379–386, https://doi.org/10.1016/j.biortech.2015.03.137.

[116] S.C. Lee, Removal and recovery of acetic acid and two furans during sugar purification of simulated phenols-free biomass hydrolysates, Bioresour. Technol. 245 (2017) 116–122, https://doi.org/10.1016/j.biortech.2017.08.206.

[117] X.F. Chen, L.Q. Zhang, W.P. Xu, C. Wang, H.L. Li, L. Xiong, H.R. Zhang, X. D. Chen, Synthesis of polyacrylamide/polystyrene interpenetrating polymer networks and the effect of textural properties on adsorption performance of fermentation inhibitors from sugarcane bagasse hydrolysate, Bioresour. Technol. 318 (2020) 124053, https://doi.org/10.1016/j.biortech.2020.124053.

[118] Y. Gong, Y. Tang, X.L. Wang, L.X. Yu, D.H. Liu, The possibility of the desalination of actual 1,3-propanediol fermentation broth by electrodialysis, Desalination 161 (2004) 169–178, https://doi.org/10.1016/S0011-9164(04)90052-5.

[119] R.C. Wu, H.J. Ren, Y.Z. Xu, D.H. Liu, The final recover of salt from 1,3-propanadiol fermentation broth, Sep. Purif. Technol. 73 (2010) 122–125, https://doi.org/10.1016/j.seppur.2010.03.013.

[120] J.W. Lee, L.T.P. Trinh, H.J. Lee, Removal of inhibitors from a hydrolysate of lignocellulosic biomass using electrodialysis, Sep. Purif. Technol. 122 (2014) 242–247, https://doi.org/10.1016/j.seppur.2013.11.008.

[121] C. Kundu, L.T.P. Trinh, H.J. Lee, J.W. Lee, Bioethanol production from oxalic acid-pretreated biomass and hemicellulose-rich hydrolysates via a combined detoxification process, Fuel 161 (2015) 129–136, https://doi.org/10.1016/j.fuel.2015.08.045.

[122] L.T.P. Trinh, C. Kundu, J.W. Lee, H.J. Lee, An integrated detoxification process with electrodialysis and adsorption from the hemicellulose hydrolysates of yellow poplars, Bioresour. Technol. 161 (2014) 280–287, https://doi.org/10.1016/j.biortech.2014.03.042.

[123] V. Kumar, M. Krishania, P. Preet Sandhu, V. Ahluwalia, E. Gnansounou, R. S. Sangwan, Efficient detoxification of corn cob hydrolysate with ion-exchange resins for enhanced xylitol production by *Candida tropicalis* MTCC 6192, Bioresour. Technol. 251 (2018) 416–419, https://doi.org/10.1016/j.biortech.2017.11.039.

[124] Y.Y. Liao, V.C. Nguyen, N. Ishiguro, A.P. Young, C.K. Tsung, K.C.W. Wu, Engineering a homogeneous alloy-oxide interface derived from metal-organic frameworks for selective oxidation of 5-hydroxymethylfurfural to 2,5-furandicarboxylic acid, Appl. Catal. B 270 (2020) 118805, https://doi.org/10.1016/j.apcatb.2020.118805.

[125] S.P. Lin, T.C. Kuo, H.T. Wang, Y.W. Ting, C.W. Hsieh, Y.K. Chen, H.Y. Hsu, K. C. Cheng, Enhanced bioethanol production using atmospheric cold plasma-assisted detoxification of sugarcane bagasse hydrolysate, Bioresour. Technol. 313 (2020), 123704, https://doi.org/10.1016/j.biortech.2020.123704.

[126] A. Petersson, J.R.M. Almeida, T. Modig, K. Karhumaa, B. Hahn-Hägerdal, M. F. Gorwa-Grauslund, G. Lidén, A 5-hydroxymethyl furfural reducing enzyme encoded by the *Saccharomyces cerevisiae* ADH6 gene conveys HMF tolerance, Yeast 23 (2006) 455–464, https://doi.org/10.1002/yea.1370.

[127] N. Wierckx, F. Koopman, H.J. Ruijssenaars, J.H. de Winde, Microbial degradation of furanic compounds: biochemistry, genetics, and impact, Appl. Microbiol. Biotechnol. 92 (2011) 1095–1105, https://doi.org/10.1007/s00253-011-3632-5.

[128] F. Hollmann, I.W.C.E. Arends, K. Buehler, A. Schallmey, B. Bühler, Enzyme-mediated oxidations for the chemist, Green Chem. 13 (2011) 226–265, https://doi.org/10.1039/c0gc00595a.

[129] X.Y. Zhang, M.H. Zong, N. Li, Whole-cell biocatalytic selective oxidation of 5-hydroxymethylfurfural to 5-hydroxymethyl-2-furancarboxylic acid, Green Chem. 19 (2017) 4544–4551, https://doi.org/10.1039/c7gc01751k.

[130] H. Ran, J. Zhang, Q.Q. Gao, Z.L. Lin, J. Bao, Analysis of biodegradation performance of furfural and 5-hydroxymethylfurfural by *Amorphotheca resinae* ZN1, Biotechnol. Biofuels 7 (2014) 51, https://doi.org/10.1186/1754-6834-7-51.

[131] D.X. Zhang, Y.L. Ong, Z. Li, J.C. Wu, Biological detoxification of furfural and 5-hydroxyl methyl furfural in hydrolysate of oil palm empty fruit bunch by *Enterobacter sp.* FDS8, Biochem. Eng. J. 72 (2013) 77–82, https://doi.org/10.1016/j.bej.2013.01.003.

[132] T.K. Godan, R.O. Rajesh, P.C. Loreni, A. Kumar Rai, D. Sahoo, A. Pandey, P. Binod, Biotransformation of 5-hydroxymethylfurfural by *Acinetobacter oleivorans* S27 for the synthesis of furan derivatives, Bioresour. Technol. 282 (2019) 88–93, https://doi.org/10.1016/j.biortech.2019.02.125.

[133] J. Švitel, P. Kútnik, Potential of acetic acid bacteria for oxidation of low-molecular monoalcohols, Lett. Appl. Microbiol. 20 (2008) 365–368, https://doi.org/10.1111/j.1472-765X.1995.tb01322.x.

[134] M. Sayed, S.H. Pyo, N. Rehnberg, R. Hatti-Kaul, Selective oxidation of 5-hydroxymethylfurfural to 5-hydroxymethyl-2-furancarboxylic acid using gluconobacter oxydans, ACS Sustain. Chem. Eng. 7 (2019) 4406–4413, https://doi.org/10.1021/acssuschemeng.8b06327.

[135] C.H. Ra, G.T. Jeong, M.K. Shin, S.K. Kim, Biotransformation of 5-hydroxymethylfurfural (HMF) by *Scheffersomyces stipitis* during ethanol fermentation of hydrolysate of the seaweed *Gelidium amansii*, Bioresour. Technol. 140 (2013) 421–425, https://doi.org/10.1016/j.biortech.2013.04.122.

[136] M.T. Guarnieri, M. Ann Franden, C.W. Johnson, G.T. Beckham, Conversion and assimilation of furfural and 5-(hydroxymethyl)furfural by *Pseudomonas putida* KT2440, Metab. Eng. Commun. 4 (2017) 22–28, https://doi.org/10.1016/j.meteno.2017.02.001.

[137] B. Singh, A. Verma, P.K. PoojaMandal, S. Datta, A biotechnological approach for degradation of inhibitory compounds present in lignocellulosic biomass hydrolysate liquor using *Bordetella sp*, BTIITR. Chem. Eng. J. 328 (2017) 519–526, https://doi.org/10.1016/j.cej.2017.07.059.

[138] B. Singh, P. Kumar, A. Yadav, S. Datta, Degradation of fermentation inhibitors from lignocellulosic hydrolysate liquor using immobilized bacterium, *Bordetella sp*, BTIITR. Chem. Eng. J. 361 (2019) 1152–1160, https://doi.org/10.1016/j.cej.2018.12.168.

[139] Y. He, J. Zhang, J. Bao, Acceleration of biodetoxification on dilute acid pretreated lignocellulose feedstock by aeration and the consequent ethanol fermentation evaluation, Biotechnol. Biofuels 9 (2016) 19, https://doi.org/10.1186/s13068-016-0438-9.

[140] F. d'Acunzo, P. Baiocco, M. Fabbrini, C. Galli, P. Gentili, A mechanistic survey of the oxidation of alcohols and ethers with the enzyme laccase and its mediation by TEMPO, Eur. J. Org. Chem. 24 (2002) 4195–14021, https://doi.org/10.1002/1099-0690(200212)2002:243.0.CO;2-X.

[141] J. Ihssen, R. Reiss, R. Luchsinger, L. Thöny-Meyer, M. Richter, Biochemical properties and yields of diverse bacterial laccase-like multicopper oxidases expressed in *Escherichia coli*, Sci. Rep. 5 (2015) 10465, https://doi.org/10.1038/srep10465.

[142] C.Y. Zhang, X. Chang, L. Zhu, Q.G. Xing, S.P. You, W. Qi, R.X. Su, Z.M. He, Highly efficient and selective production of FFCA from CotA-TJ102 laccase-catalyzed oxidation of 5-HMF, Int. J. Biol. Macromol. 128 (2019) 132–139, https://doi.org/10.1016/j.ijbiomac.2019.01.104.

[143] D. Singh, S. Chen, The white-rot fungus *Phanerochaete chrysosporium*: Conditions for the production of lignin-degrading enzymes, Appl. Microbiol. Biotechnol. 81 (2008) 399–417, https://doi.org/10.1007/s00253-008-1706-9.

[144] M. Hofrichter, Review: Lignin conversion by manganese peroxidase (MnP), Enzyme Microb. Technol. 30 (2002) 454–466, https://doi.org/10.1016/S0141-0229(01)00528-2.

[145] K.L. Yee, L.E. Jansen, C.A. Lajoie, M.H. Penner, L. Morse, C.J. Kelly, Furfural and 5-hydroxymethyl-furfural degradation using recombinant manganese peroxidase, Enzyme Microb. Technol. 108 (2018) 59–65, https://doi.org/10.1016/j.enzmictec.2017.08.009.