INTRODUCTION

Bacterial cellulose (BC) is an organic compound synthesized by various bacteria such as *Gluconacetobacter*, *Agrobacterium*, *Salmonella*, and *Pseudomonas* (Jonas & Farah, 1998), and *Gluconacetobacter xylinus* is well known as one of the most effective BC producers (Yang et al., 2019). Contrary to conventional plant cellulose, BC is secreted without any byproducts (e.g., hemicellulose and lignin) and thus features high purity, comprising 2 to 4 nm diameter nanofibrils bundled.
into 60 nm diameter nanoribbons and thus exhibiting high crystallinity, high mechanical strength, water capacity, and biocompatibility (Cannon & Anderson, 1991; Yamanaka et al., 1989). Consequently, BC finds numerous applications in cosmetics, dietary foods (Azeredo et al., 2019; Shi et al., 2014), cosmetics (Hasan et al., 2012; Pacheco, de Mello, et al., 2017), and biomaterials (Ciechanska, 2004; Czaja et al., 2006; Ul-Islam et al., 2020; Zang et al., 2015). As regard the field of biomaterials, companies such as Biofill® and Bioprocess® have launched BC-based wound healing patches with superior biocompatibility, transparency, and exudate absorption ability (Czaja et al., 2006). Additionally, BC composites such as chitosan-BC and polyurethane-BC can be employed for biosensing (Wang et al., 2010) wound healing (Lin et al., 2013), and flexible display fabrication (Umartyotin et al., 2012). However, industrial BC production is hindered by high operation costs, which has inspired investigations on the use of feedstocks such as agro-forest residue (Carreira et al., 2011), wheat straw (Hong et al., 2011), crude glycerol from biodiesel production (Yang et al., 2019), cashew tree residue (Pacheco, Nogueira, et al., 2017), and thin stillage (Revin et al., 2018).

Lignocellulosic biomass, one of the most earth-abundant materials that can be obtained as agricultural, forest, and industrial residues, has a carbohydrate (mainly cellulose, hemicellulose, and lignin) content of ~70 wt% and contains fermentable sugar, therefore being a cost-effective fermentation feedstock for the production of value-added products such as biofuel, biochemicals, biomaterials, and enzymes (Banerjee et al., 2019; Lien et al., 2019; Park et al., 2018; Siripong et al., 2018). Efficient utilization of lignocellulosic biomass requires enzymatic saccharification to obtain fermentable sugars. However, the rigid association between cellulose, hemicellulose, and lignin results in low cellulose surface accessibility to enzymes and hinders efficient conversion, which highlights the need for pretreatment to disrupt the rigid crystalline structure and increase the sugar yield of saccharification (Morone et al., 2018; Sun et al., 2016; Trinh et al., 2018).

Under the harsh pretreatment conditions, the formation of fermentable sugars is accompanied by that of inhibitors, which can be classified into aliphatic (e.g., acetic, formic, and levulinic) acids, furans (5-hydroxymethylfurural [5-HMF] and furfural), and phenolics. Aliphatic acids, generated by the decomposition of pentoses, hexoses, and furans (e.g., acetic acid is produced by the deacetylation of xylan, and formic acid is produced by furan decomposition), can penetrate the cell membrane and be ionized inside the cell, which results in an intracellular pH drop and ATP depletion. Furan produced by sugar dehydration (e.g., 5-HMF and furfural are formed by dehydration of hexoses and pentoses, respectively) is known to affect the intracellular NAD+/NADH ratio by oxidation of 5-HMF and furfural, and metabolic pathways are inhibited due to the lack of intracellular NAD+. Phenolics, generated via lignin structure breakdown, are known to be more toxic than aliphatic acids and furans, strongly inhibiting cell activity at relatively low concentrations and damaging the cell membrane because of its hydrophobicity (Jönsson & Martin, 2016; Kim, 2018). Previous studies on the inhibitory effect of compounds derived from lignocellulosic biomass mainly focused on ethanol production by Escherichia coli, Zymomonas mobilis and 2,3-butanediol production by Enterobacter aerogenes and Klebsiella pneumoniae, whereas the effect of specific lignocellulose-derived inhibitors on the activity of G. xylinus remains underexplored (Joo et al., 2016; Lee et al., 2015).

Herein, we investigated the inhibitory effects of aliphatic (acetic and formic) acids, furans (5-HMF and furfural), and phenolics (p-coumaric acid and syringaldehyde) on BC production by G. xylinus, and of the produced BC from three different lignocellulosic hydrolysates to obtain information regarding pretreatment and biomass selection for efficient BC production.

## 2 MATERIALS AND METHODS

### 2.1 Strain, medium, and hydrolysates

Glucocacetobacter xylinus ATCC 53524 used for BC production was stored in YPD agar at 4°C. The seed medium (YPD) contained 10 g/L yeast extract, 20 g/L peptone, and 20 g/L dextrose. The culture medium used for BC production (BCEL-GC01), which was prepared by modifying the carbon source concentration of the Zhou medium (Zhou et al., 2007), contained 50 g/L glucose as a carbon source, 20 g/L corn steep liquor (CSL), 4 g/L ammonium sulfate, 2 g/L dibasic potassium phosphate, and 0.4 g/L magnesium sulfate heptahydrate.

Inhibitor concentrations used to investigate the effect of lignocellulosic biomass hydrolysates on G. xylinus were as follows: 2–10 g/L acetic acid, 0.25–1.25 g/L formic acid, 1–4 g/L 5-HMF, 0.1–0.5 g/L furfural, 0.5–2.5 g/L p-coumaric acid, and 0.5–2.5 g/L syringaldehyde. All media were adjusted to pH 6.0 with 1 M HCl and NaOH.

### 2.2 Preparation of lignocellulosic hydrolysates

Three lignocellulosic biomass hydrolysates (Miscanthus, barley straw, and pine tree) were hydrothermally pretreated in the presence of H$_2$SO$_4$ as a catalyst, and obtained mixtures were detoxified by adsorption on activated carbon (Guo et al., 2013). The hydrolysis of the pretreated biomass was performed using Cellic CTec2 (Novozymes) as an enzyme
complex, and the enzyme reaction was carried out at 50°C and pH 4.8 for 72 h. For production of BC from hydrolysates, the pretreated hydrolysates were diluted with distilled water to bring the concentration of glucose in the hydrolysates to 50 g/L, following which 20 g/L CSL, 4 g/L ammonium sulfate, 2 g/L dibasic potassium phosphate, and 0.4 g/L magnesium sulfate heptahydrate were added to the hydrolysates.

2.3 | BC production and purification

Seed culturing was performed at 30°C for 24 h on a shaker platform at 150 rpm in a 250 ml Erlenmeyer flask with 100 ml of YPD medium, and was followed by inoculation into BCEL-GC01 medium at 4 vol%. The main cultivation was carried out statically in a 250 ml Erlenmeyer flask with 50 ml of BCEL-GC01 medium at 30°C for 7 days. After cultivation, BC was harvested and washed several times with distilled water, washed with 1 N NaOH to remove residual medium and cell debris, washed with distilled water again, and dried at 60°C overnight. BC production [g/L] was calculated as BC mass [g]/volume of culture medium [L].

BC production [g/L] = \frac{\text{Mass of BC [g]}}{\text{Volume of culture medium [L]}}.

2.4 | Analytical methods

The concentration of phenolics was determined by the Folin–Ciocalteu method (Singleton et al., 1999). A 20 μl sample aliquot was diluted 80-fold with distilled water, treated with 100 μl of the Folin–Ciocalteu reagent (Sigma-Aldrich), and allowed to react for 8 min. Subsequently, 300 μl of 30 wt% Na₂CO₃ solution was added, and absorbance at 765 nm was measured on a UV/VIS spectrophotometer (Shimadzu, UV-1800) after 60 min. Gallic acid was used to construct a calibration curve.

Chemical and surface properties of BC were analyzed by Fourier transform infrared (FTIR) spectroscopy (JASCO FTIR-4600) and scanning electron microscopy (SEM; SEN-3000M, SEC Co., Ltd.; 15 kV, 15,000×).

3 | RESULTS AND DISCUSSION

3.1 | Effect of aliphatic acid

Figure 1 shows the effects of acetic and formic acids on BC production. For the control (inhibitor-free) sample, BC production was determined as 17.07 g/L, while the value obtained at 2 g/L of acetic acid was slightly higher (18.10 g/L). However, BC production declined over 4 g/L of acetic acid, reaching a value of 7.73 g/L (45.3% of the control value) at 10 g/L (Figure 1a). Low concentrations (0.25 and 0.50 g/L) of formic acid improved BC production to 17.90 and 17.66 g/L, respectively. However, at ≥0.75 g/L formic acid, BC production was suppressed (Figure 1b).

In general, aliphatic acids are known to cause ATP depletion and interfere with cell growth, as outlined above. Moreover, carboxylate anions produced upon acid ionization can be accumulated and are cytotoxic.

Bacteria of the *Gluconacetobacter* genus have been used in vinegar production and are therefore resistant to acetic acid, utilizing it (at lower-than-threshold levels) as a carbon source to improve BC production (Toda et al., 1997). Jung et al. (2010) reported that low concentrations of acetic acid (up to 1 vol%) enhance BC production by *G. xylinus*, and Son et al. (2001) showed that acetic acid increased BC production by *G. xylinus* at a level of 0.2 vol%. As the metabolic pathway of the above organic acids are close to the tricarboxylic acid cycle, these compounds can be utilized as carbon sources and stimulate cell growth (Keshk & Samechima, 2005; Son et al., 2001; Zhong et al., 2013). However, at high acetic acid
concentrations, BC production decreased because of the general toxicity of aliphatic acids. Lee et al. (2015) demonstrated that up to a certain level, acetic acid enhances the production of 2,3-butanediol by *Enterobacter aerogenes* by increasing the activity of the corresponding enzyme, whereas toxicity observed at overly high concentrations results in decreased diol production.

Zhang, Winestrand, Chen, et al. (2014) reported that *G. xylinus* can uptake 25 mM (1.15 g/L) formic acid, demonstrating that low formic acid concentrations did not enhance BC production compared to the case of acetic acid. Besides, at levels of >100 mM (4.6 g/L), BC production was suppressed. Zaldivar and Ingram revealed that organic acids (including formic acid) hinder the growth of *E. coli*, further showing that dissociated anions cause the leakage of Mg$^{2+}$ resulting in cell membrane damage. With increasing organic acid concentration, dissociated anions progressively accumulate and damage membrane integrity (Zaldivar & Ingram, 1999). Larsson et al. (1999) also reported that the dissociated anion exhibits cytotoxicity.

Formic acid inhibits BC production similarly to acetic acid, but is more toxic, featuring a $pK_a$ (3.75 at 20°C) that is lower than those of levulinic (4.66) and acetic (4.75) acids. Therefore, formic acid dissociates and diffuses more easily than the above acids at a given pH, thus exhibiting higher toxicity due to anion accumulation (Almeida et al., 2007).

### 3.2 Effect of furan compounds

The effect of 5-HMF on BC production is shown in Figure 2. Compared to that in the control sample, BC production in samples containing 5-HMF decreased to 14.92, 8.30, 4.99, and 0.43 g/L at inhibitor levels of 1, 2, 3, and 4 g/L, respectively (Figure 2a). A similar trend was observed for furfural, that is, BC production was determined as 16.84, 16.20, and 15.65 g/L at furfural concentrations of 0.1, 0.2, and 0.3 g/L, respectively. At an inhibitor level of 0.4 g/L, BC production further decreased to 0.40 g/L and was completely suppressed at furfural levels of >0.5 g/L (Figure 2b).

Furans are known to affect the NAD$^+/\text{NADH}$ ratio and thus inhibit cell growth and essential metabolic pathways such as glycolysis. 5-HMF can be reduced to 5-hydroxymethylfurfural alcohol or oxidized to 5-hydroxymethylfuroic acid (Larsson et al., 1999), which, in combination with other redox processes, can influence certain metabolic pathways. Zaldivar et al. (1999) reported the effects of aldehydes on *E. coli* LY01, revealing that these species (e.g., 5-HMF and furfural) inhibit cell growth and ethanol production, with the toxicity of 5-HMF being less than that of furfural.

Similarly, furfural reduction to furfuryl alcohol or oxidation to 2-furoic acid can also affect the levels of NAD$^+$ and NADH. Roberto et al. (1991) reported that furfural inhibits ethanol production by *Pichia stipitis* and prolongs the lag phase by 15–20 h, strongly inhibiting cell growth at levels of ≥2 g/L (Roberto et al., 1991). The effect of furfural on ethanol production by *S. cerevisiae* was also investigated by Taherzadeh, Gustafsson, Nikalasson, Liden (2000), who revealed that yeast such as *Pichia stipitis* and *S. cerevisiae* can reduce furfural to furfuryl alcohol, which results in high NADH consumption and thus stimulates other oxidation pathways including the oxidation of ethanol to acetaldehyde, interfering with ethanol production and influencing critical cellular pathways. The oxidation of furfural to 2-furoic acid also hinders cell growth, for example, Wordofa and Kristensen (2018) reported that the lag phase of *Pseudomonas taiwanensis* was prolonged by 2.3, 7.58, and 24 h in the presence of 1, 2, and 3 g/L furfural, respectively. The oxidation of furfural to 2-furoic acid is dependent on NAD$^+$, increasing the demand for NAD$^+$ and thus interfering with essential metabolic pathways such as glycolysis and inhibiting cell growth. Although 2-furoic acid is less toxic than furfural, the former can also inhibit cell growth and the bioproduction of
certain chemicals, as reported by Zaldivar and Ingram (1999). Moreover, furfural is known to affect DNA, for example, Allen et al. (2010) reported that furfural promotes the accumulation of activated oxygen in *S. cerevisiae* and damages mitochondria and vesicle membranes.

In the case of *G. xylinus*, both 5-HMF and furfural hindered cell growth and reduced BC production, which was ascribed to the lack of NAD⁺ caused by the oxidation of 5-HMF to 5-hydroxymethylfuroic acid and that of furfural to 2-furoic acid. The elevated consumption of NAD⁺ probably affected NAD⁺-dependent pathways such as glucose metabolism and BC production (Zhang, Winestrand, Chen, et al., 2014; Zhang, Winestrand, Guo, et al., 2014).

### 3.3 Effect of phenolic compounds

In general, phenolics produced from lignin degradation are more toxic than inhibitors produced during lignocellulosic biomass processing. Low-molecular-weight phenolics are stronger inhibitors than high-molecular-weight ones, as the former can easily penetrate cell membranes and damage their structure. It is known that the toxicity or tolerance to phenolics depends on the microbial strain. *G. xylinus* has been reported to have relatively higher tolerance than strains such as *Saccharomyces cerevisiae*, *Candida utilis*, and *K. pneumoniae* (Zhang, Winestrand, Guo, et al., 2014).

Figure 3 presents the effects of *p*-coumaric acid and syringaldehyde. As the concentration of *p*-coumaric acid progressively increased to 0.5, 1, 1.5, 2, and 2.5 g/L, BC production decreased to 16.40, 15.82, 10.35, 1.08, and 0.23 g/L, respectively (Figure 3a). A similar trend was observed for syringaldehyde, with BC productions of 16.21, 14.95, 13.28, 9.02, and 2.52 g/L determined for inhibitor levels of 0.5, 1.0, 1.5, 2.0, and 2.5 g/L, respectively (Figure 3b). Both *p*-coumaric acid and syringaldehyde could penetrate the cell membrane because of its hydrophobicity and thus reduce membrane integrity and hinder cell growth.

According to Mills et al. (2009), *p*-coumaric acid can penetrate the cell membrane, inhibit the metabolism of intracellular hydrophobic compounds, and reduce enzyme activity, additionally causing partial membrane leakage and membrane structure damage. Joo et al. (2016) reported that at a level of 0.5 g/L, *p*-coumaric acid reduced production of 2,3-butanediol by *E. aerogenes* to 14% of the control value and decreased cell growth to 37% of the control value, with complete suppression of diol production observed at a level of 1 g/L.

Syringaldehyde has a similar inhibitory mechanism with *p*-coumaric acid although the aromatic aldehyde causes relatively no significant cell membrane damage compared to the aromatic acid (Mills et al., 2009). Zaldivar et al. (2000) demonstrated that syringaldehyde inhibits the growth of *E. coli* LY01 and reduces the corresponding ethanol production while Franden et al. (2013) showed that the growth of *Zymomonas mobilis* is strongly inhibited at concentrations of 100 mM *p*-coumaric acid and 40 mM syringaldehyde.

In case of *G. xylinus*, both aromatic acids and aldehydes interfere with cell growth and reduce BC production, for example, Zhang, Winestrand, Guo, et al. (2014) revealed that BC production sharply decreases to 43% of the control value at a coniferyl aldehyde level of 0.35 g/L and is completely inhibited at a vanillin concentration of 0.38 g/L, whereas 4-hydroxybenzoic acid showed a relatively weak inhibitory effect at the same concentration.

### 3.4 BC production from lignocellulosic hydrolysates

To explore the possibility of BC production, we investigated the possibility of three pretreated lignocellulosic biomasses (*Miscanthus*, barley straw, and pine tree), revealing the presence of glucose (approximately 50 g/L), acetic acid...
(0.059–0.128 g/L), formic acid (0.081–0.157 g/L), 5-HMF (0.041–0.129 g/L), furfural (0.010–0.016 g/L), and phenolics (total phenolics content (TPC) = 0.110–0.350 g/L; Table 1).

Although the initial BC production was relatively slow when biomass was used compared to the control, BC production was almost completed on the 5th day and the maximum production of BC was shown on the 7th day. After the 7th day, there was little change in production (data not shown). The highest BC production (16.70 g/L, 97.86% of the control group) in the experimental group was observed in Miscanthus hydrolysate, with about twofold higher aliphatic acid content (0.13 g/L of acetic acid and 0.16 g/L of formic acid) than the other two biomass hydrolysates. Although the TPC of this hydrolysate was the highest, it was sufficiently low not to interfere with BC production. Lee and Kuan (2015) reported that Miscanthus of South Korean origin contains 37 wt% cellulose, 27 wt% hemicellulose, and 18 wt% lignin, revealing that almost 65% of cellulose and hemicellulose can be converted to fermentable sugar suitable for BC production by G. xylinus. In addition, the initial glucose concentration of Miscanthus hydrolysate is about 2 g/L higher than the other two biomasses, which may cause the BC production to be slightly higher. The BC production obtained for barley straw hydrolysate (13.09 g/L) equaled 76.66% of the control, and the aliphatic acid concentration therein was sufficiently high to enhance BC production. Similar results were obtained for pine tree hydrolysate (BC production = 12.54 g/L, 73.45% of the control; Figure 4).

The BC productions of the three hydrolysates are above 70% of the control value. After pretreatment of lignocellulosic biomass, the composition of sugar can also affect microbial growth and product yield during fermentation. In general, various types of sugars are produced through pretreatment and detoxification, such as glucose, xylose, galactose, ramnos, and mannose. The composition and concentration of sugar can vary depending on the biomass pretreatment method. Guo et al. (2013) examined BC production from spruce hydrolysates detoxified by 10 different methods. The BC production of the reference medium equaled 7.5 g/L, whereas no BC was produced from non-pretreated hydrolysate. Only four hydrolysates treated using activated carbon adsorption, overliming, anion exchange at pH 10, and anion exchange at pH 5 showed non-zero BC production. The BC production of the activated carbon-treated hydrolysate (8.2 g/L) and anion exchange at pH 10 treated hydrolysate (7.9 g/L) exceeded the control value, which also indicated the high efficiency of this pretreatment for reducing inhibitor content, particularly in cases of furans and phenolics (removal efficiency >85%). The activated carbon-treated hydrolysate contained higher sugars and showed higher BC production than the anion exchange in the pH 10 treated hydrolysate.

Although many studies have been investigated the effects of biomass-derived inhibitors on the value-added chemical production, there are phenomena that are not clearly explained due to the relationship between complex components and unconfirmed components. To efficiently utilize various biomass, continuous efforts to solve this problem are required.

### 3.5 Chemical and surface properties of BC

Chemical and surface properties of BC derived from the control and three hydrolysates were analyzed by FTIR and SEM. The FTIR spectra of BC (400–4000 cm⁻¹) revealed the presence of O–H, C–H, and C–O–C units (Figure 5). Peaks at

| TABLE 1 Composition and BC production of the three lignocellulosic biomass hydrolysates |
|----------------------------------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|
|                                | Glucose (g/L) | Xylose (g/L) | Acetic acid (g/L) | Formic acid (g/L) | Furfural (g/L) | 5-HMF (g/L) | Total phenol content (g/L) | BC production (g/L) | Relative BC production (%) |
| Control                         | 50         | 0         | —         | —         | —         | —         | —         | 17.07                   | 100.00              |
| Miscanthus                      | 52.81      | 2.04      | 0.128 ± 0.010 | 0.157 ± 0.010 | 0.016 ± 0.007 | 0.047 ± 0.002 | 0.350 ± 0.024 | 16.70                   | 97.86               |
| Barley straw                    | 50.54      | 2.97      | 0.047 ± 0.003 | 0.081 ± 0.001 | 0.012 ± 0.001 | 0.129 ± 0.001 | 0.283 ± 0.004 | 13.09                   | 76.66               |
| Pine tree                       | 50.83      | 1.398     | 0.059 ± 0.002 | 0.083 ± 0.003 | 0.010 ± 0.002 | 0.041 ± 0.003 | 0.110 ± 0.004 | 12.54                   | 73.50               |

![Figure 4](BC production from three lignocellulosic hydrolysates)
3351 and 2974 cm$^{-1}$ were ascribed to O–H and C–H stretching vibrations, respectively, with strong signals at 1388 and 1050 cm$^{-1}$ attributed to C–H bending and C–O stretching, respectively. The weak band at 1160 cm$^{-1}$ indicated C–O–C asymmetric stretching, and that at 870 cm$^{-1}$ was characteristic of cellulose β-glycosidic linkages. Thus, FTIR spectroscopy showed that BC obtained from lignocellulosic biomass hydrolysates and the control had similar chemical properties.

The SEM image of BC from the control and three hydrolysates is shown in Figure 6, and all showed that it contained an ultrafine network of numerous nanofibrils. It was observed that the image of BC derived from the control, barley straw, and pine tree hydrolysate were tightly packed and showed similar arrangement (Figure 6a, c, d). However, it can be observed that the nanofibrils of BC from Miscanthus hydrolysate was a relatively distant arrangement (Figure 6b). It is expected that the hydrolysate of biomass for BC production could affect the nanofiber arrangement.

4 | CONCLUSION

Herein, we investigated the effects of lignocellulosic biomass–derived inhibitors (aliphatic acids, furans, and phenolics) on BC production from three (Miscanthus, barley straw, and pine tree) pretreated lignocellulosic hydrolysates, revealing the promotional effects of aliphatic acids at low concentrations (2 g/L of acetic acid and 0.50 g/L of formic acid). However, furans, phenolics, and high concentrations of aliphatic acids inhibited BC production. For all three hydrolysates, BC production was at least 70% of the control value, which confirmed the possibility of efficient BC production from lignocellulosic biomass. Moreover, this study provides valuable information regarding the effects of lignocellulosic inhibitors on G. xylinus and the strategy of biomass application for the production of BC.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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