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An oxidoreductase gene *ZMO1116* enhances the *p*-benzoquinone biodegradation and chiral lactic acid fermentability of *Pediococcus acidilactici*

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ABSTRACT

p-Benzoquinone (BQ) is a lignin-derived inhibitor to microbial strains. Unlike the furan inhibitors, *p*-benzoquinone is recalcitrant to traditional detoxification methods. This study shows a biological degradation of *p*-benzoquinone and a simultaneous D-lactic acid fermentation by an engineered *Pediococcus acidilactici* strain. The overexpression of an oxidoreductase gene *ZMO1116* from *Zymomonas mobilis* encoding oxidoreductase was identified to improve the D-lactic acid fermentability of *P. acidilactici* against *p*-benzoquinone. The gene *ZMO1116* was integrated into the genome of *P. acidilactici* and enabled the engineered *P. acidilactici* to convert *p*-benzoquinone into less toxic hydroquinone (HQ), resulting in the improved *p*-benzoquinone tolerance. Simultaneous saccharification and co-fermentation (SSCF) was conducted using the pretreated and biodetoxified corn stover containing *p*-benzoquinone, the D-lactic acid production of the engineered strain (123.8 g/L) was 21.4 % higher than the parental strain (102.0 g/L). This study provides a practical method on robust *p*-benzoquinone tolerance and efficient cellulosic chiral lactic acid fermentation from lignocellulose feedstock.

1. Introduction

Pretreatment is the core step in lignocellulose biorefinery processes, but various inhibitors were inevitably generated during harsh pretreatment (Jönsson et al., 2013; Meng and Ragauskas, 2014). Besides the furan aldehydes (furfural and 5-hydroxymethylfurfural), weak acids (acetic acid, formic acid, and levulinic acid), and phenolic aldehydes (4-hydroxybenaldehyde, vanillin, and syringaldehyde), *p*-benzoquinone (BQ) is also a harsh inhibitor on enzymatic hydrolysis and fermentation processes. *p*-Benzoquinone is generated from the oxidation of *p*-hydroxyphenyl compounds of 4-hydroxybenaldehyde, 4-hydroxybenzyl alcohol and 4-hydroxybenzoic acid (Saa et al., 1986), which performs the high toxicity to microbe cells by increasing reactive oxygen species (ROS) level, oxidizing DNA and breaking DNA double strands (Lee et al., 2002; Philbrook and Winn, 2015). Only 20−60 mg/L of *p*-benzoquinone completely inhibit the cell growth and ethanol production of *Saccharomyces cerevisiae* cells (Larsson et al., 2000; Stagge et al., 2015; Yan et al., 2019). When *p*-benzoquinone is at 100 mg/L, the lactic acid producing strain *P. acidilactici* TY112 is strongly and negatively affected (Yan et al., 2019).

Conventional detoxification methods (water washing and biodetoxification) do not work well on removal of *p*-benzoquinone. *p*-Benzoquinone can be removed from the pretreated lignocellulose feedstock by water washing and prolonged biodetoxification, however, considerable fermentable sugars in the pretreated lignocellulose were lost and resulted in poor biochemicals production (Yan et al., 2019). For retaining the fermentable sugars, the *p*-benzoquinone residue was inevitably remained in the lignocellulose feedstock and negatively affected the fermentation step. This leads to a contradiction: complete removal of *p*-benzoquinone results in the big loss of fermentable sugars, and reservation of fermentable sugars leads to the residue of *p*-benzoquinone and consequently reduces the fermentation efficiency. To solve this issue, we propose to apply the fermenting strain to simultaneously complete the biological conversion of the residual *p*-benzoquinone into its less toxic alcohol-derivative hydroquinone (HQ) (Yan et al., 2019) and the production of biochemical during fermentation step.

Lactic acid is a widely used platform chemical with high potential for production of biodegradable plastic poly-lactic acid (PLA) (de Oliveira

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Table 1
Strains, plasmids and primers used.

Strains	Characteristics	Sources
E. coli XLI-blue	Host for plasmid construction	Stratagene
A. resinae ZN1	Biodetoxification fungus isolated in our lab	Zhang et al. (2010)
Z. mobilis ZM4	The *p*-benzoquinone tolerant genes contained strain	ATCC
P. acidilactici ZY15	Glucose and xylose co-fermenting strain for D-lactic acid production	Qiu et al. (2017)
P. acidilactici ZY15 (pZY36e)	*P. acidilactici* ZY15 harboring empty plasmid pZY36e	Qiu et al. (2020)
P. acidilactici ZY15 (pZY36e-*ZMO1116*)	*P. acidilactici* ZY15 harboring *ZMO1116* expression plasmid	This work
P. acidilactici ZY15 (pZY36e-*ZMO1399*)	*P. acidilactici* ZY15 harboring *ZMO1399* expression plasmid	This work
P. acidilactici ZY15 (pZY36e-*ZMO1576*)	*P. acidilactici* ZY15 harboring *ZMO1576* expression plasmid	This work
P. acidilactici ZY15 (pZY36e-*ZMO1696*)	*P. acidilactici* ZY15 harboring *ZMO1696* expression plasmid	This work
P. acidilactici ZY15 (pZY36e-*ZMO1984*)	*P. acidilactici* ZY15 harboring *ZMO1984* expression plasmid	This work
P. acidilactici ZY15-Δ*ackA2*::*ZMO1116*	Integration of the expression cassette *PldhD_ZMO1116* into *ackA2* locus of *P. acidilactici* ZY15	This work
P. acidilactici ZY15-Δ*ackA2*::*ZMO1399*	Integration of the expression cassette *PldhD_ZMO1399* into *ackA2* locus of *P. acidilactici* ZY15	This work

Plasmids	Characteristics	Sources
pZY36e	Expression plasmid with *PldhD* replacing *P32* promoter of pMG36e	Qiu et al. (2020)
pZY36e-*ZMO1116*	*ZMO1116* expression plasmid	This work
pZY36e-*ZMO1399*	*ZMO1399* expression plasmid	This work
pZY36e-*ZMO1576*	*ZMO1576* expression plasmid	This work
pZY36e-*ZMO1696*	*ZMO1696* expression plasmid	This work
pZY36e-*ZMO1984*	*ZMO1984* expression plasmid	This work
pSET4E-Δ*ackA2*	Plasmid for gene *ackA2* deletion	Qiu et al. (2018)
pSET4E-Δ*ackA2*::*ZMO1116*	Plasmid for integration of *PldhD_ZMO1116* into *ackA2* locus of *P. acidilactici* ZY15	This work
pSET4E-Δ*ackA2*::*ZMO1399*	Plasmid for integration of *PldhD_ZMO1399* into *ackA2* locus of *P. acidilactici* ZY15	This work

Primers	Sequences (5′- 3′)
ZMO1116-F	GCTCTAGAATGGCGCAAAATAAAATGCTGT
ZMO1116-R	AAAACTGCAGTCAGGCAAAAACAGCTTTCTTTTTAG
ZMO1399-F	GCTCTAGAATGAACACAACTGATGCCAAGACA
ZMO1399-R	AAAACTGCAGTCAGCGGATATCCTGTATTTTATCC
ZMO1576-F	GCTCTAGAATGAACCAGAATATCCGCAATA
ZMO1576-R	AAAACTGCAGTTATAATGCCTGTTTTGTCGGT
ZMO1696-F	GCTCTAGAATGCGCGCCATAGGTTATCA
ZMO1696-R	AAAACTGCAGTTAGAAGCCTTCTAAGACGATTTTACC
ZMO1984-F	GCTCTAGAATGGATTATACGTATTTGGGTCGTAC
ZMO1984-R	AAAACTGCAGCTACCATGCATAGGCTTCAGGC
PldhD-F*	CCGCTCGAGTGCTCTGGTGTGCAGACCAGAC
ZMO1116-R*	CGCGGATCCTCAGGCAAAAACAGCTTTCTTTTTAG
ZMO1399-R*	CGCGGATCCTCAGCGGATATCCTGTATTTTATCC

Note: The underline indicates the digestion site. The asterisk indicates the primers used for integration plasmids construction.

et al., 2018). The future great need of PLA as the alternative of petroleum-based plastics certainly requires a sustainable feedstock for lactic acid production (Abdel-Rahman et al., 2011). Among various feedstocks, lignocellulose biomass is a promising option because of its availability and great abundance. In previous works, we constructed a D-lactic acid producing strain *P. acidilactici* ZY15 with a remarkable feature on co-utilizing glucose and xylose from lignocellulose feedstock (Yi et al., 2016; Qiu et al., 2017). In this study, the *p*-benzoquinone reduction conversion pathway was successfully constructed in *P. acidilactici* by genome-integration of a heterologous oxidoreductase gene. The toxic *p*-benzoquinone was reduced into less toxic hydroquinone by *P. acidilactici*, resulting in improved tolerance to *p*-benzoquinone and accelerated D-lactic acid production from corn stover. This study demonstrated the construction of *p*-benzoquinone conversion pathway in fermenting strain could efficiently improve the cellulosic D-lactic acid fermentability.

2. Materials and methods

2.1. Strains and growth conditions

The strains used are listed in Table 1. The xylose-fermenting strain *P. acidilactici* ZY15 (CGMCC 13612, Chinese General Microorganisms collection center, Beijing, China) was constructed in Qiu et al., 2017 and cultured in simplified Man-Rogosa-Sharp (MRS) medium (De Man et al., 1960) at 42 °C, 150 rpm. *Escherichia coli* XLI-blue used for plasmids construction was cultivated at 37 °C, 200 rpm in Luria-Bertani (LB) medium supplemented with 400 μg/mL erythromycin as a selection pressure. *Amorphotheca resinae* ZN1 (CGMCC 7452) for inhibitors biodetoxification was isolated in previous work and cultured at 28 °C on a potato dextrose agar (PDA) slant (Zhang et al., 2010). *Z. mobilis* ZM4 (ATCC 31821) used for the *p*-benzoquinone tolerant genes amplification was purchased from the American Type Culture Collection (ATCC, Manassas, VA, USA). The ingredients of the above MRS, LB and PDA media were described previously (Qiu et al., 2020).

2.2. Enzymes and reagents

The analytical pure *p*-benzoquinone and hydroquinone were purchased from Kamai Shu Biotech (Shanghai, China). The enzymes used for recombinant strains construction were from Takara (Otsu, Japan). Commercial cellulase Cellic CTec 2.0 was provided by Novozymes (Beijing, China), the filter paper activity (203.2 FPU/mL), cellobiase activity (4900 CBU/mL) and protein concentration (87.3 mg/mL) were measured according to Adney and Baker (1996); Ghose (1987) and Bradford (1976), respectively.

2.3. Plasmids and strains construction

All the plasmids and primers are summarized in Table 1. The genomic DNA of *Z. mobilis* ZM4 was extracted using a TIANamp bacterial DNA kit (Tiangen Biotech, Beijing, China). The genes *ZMO1116*, *ZMO1399*, *ZMO1576*, *ZMO1696* and *ZMO1984* were PCR-amplified from *Z. mobilis* genomic DNA and separately inserted into the expression plasmid pZY36e (Qiu et al., 2020). Five recombinant plasmids pZY36e-*ZMO1116*, pZY36e-*ZMO1399*, pZY36e-*ZMO1576*,

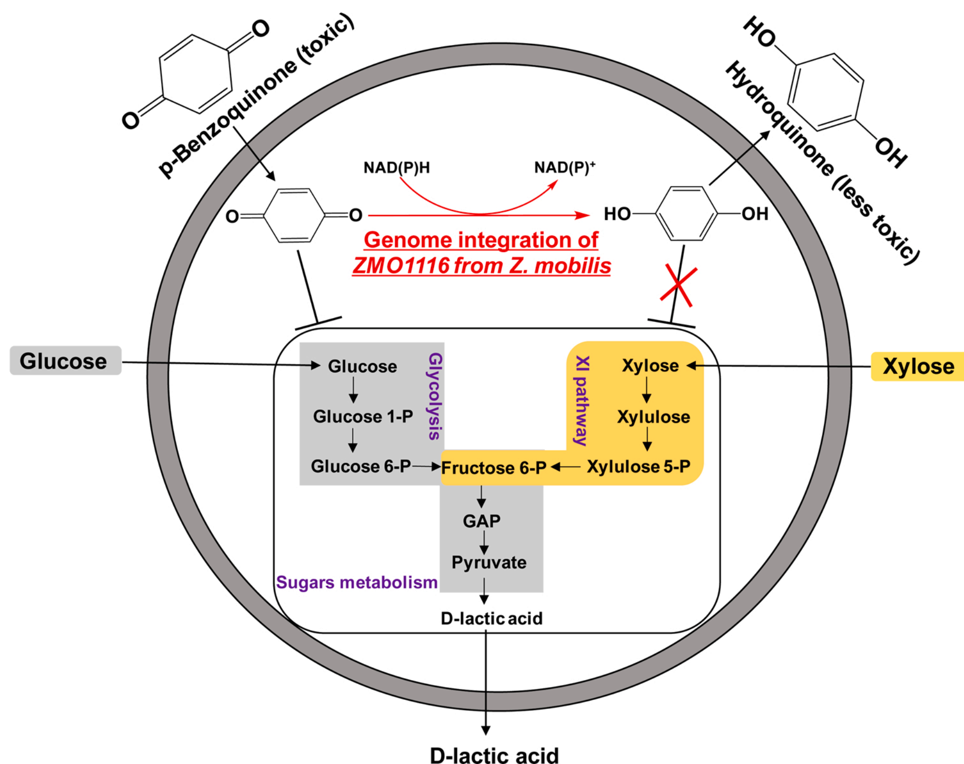

Fig. 1. *p*-Benzoquinone (BQ) conversion pathway construction in *P. acidilactici* ZY15. XI pathway represents xylose isomerase pathway.

pZY36e-*ZMO1696* and pZY36e-*ZMO1984* were obtained and then transformed into *P. acidilactici* ZY15.

The expression cassette was then inserted into the gene *ackA2* locus encoding acetate kinase for decreasing the byproduct acetic acid production, and the deletion plasmid pSET4E-Δ*ackA2* has been constructed by Qiu et al., 2018. Expression cassettes *PldhD_ZMO1116* and *PldhD_ZMO1399* were PCR-amplified from the plasmids pZY36e-*ZMO1116* and pZY36e-*ZMO1399*, respectively, and then inserted into the restriction site of *Xho* I and *BamH* I of pSET4E-Δ*ackA2*. The obtained plasmids pSET4E-Δ*ackA2*::*ZMO1116* and pSET4E-Δ*ackA2*::*ZMO1399* were separately transformed into *P. acidilactici*. The integration of *PldhD_ZMO1116* and *PldhD_ZMO1399* into *P. acidilactici* genome was performed using the protocol previously (Yi et al., 2016).

2.4. Adaptive evolution

The adaptive evolution of two engineered strains *P. acidilactici* ZY15-Δ*ackA2*::*ZMO1116* and *P. acidilactici* ZY15-Δ*ackA2*::*ZMO1399* was carried out in MRS medium supplemented with increasing *p*-benzoquinone (from 45 to 55 mg/L). *P. acidilactici* was cultivated into the *p*-benzoquinone containing MRS for 48 h, then transferred into fresh *p*-benzoquinone containing MRS at 10 % (v/v) inoculation. This continuously transfer process was repeated for 45 times (45 mg/L for 9 transfers, 50 mg/L for 14 transfers, and 55 mg/L for 22 transfers) and stopped until the D-lactic acid production remained stable. The cultured broth was maintained at pH 5–6 by adding 0.6 g $CaCO_3$ per gram glucose.

2.5. Biorefinery processing

Corn stover was harvested from Nanyang, Henan, China in spring 2018, and chopped, washed, air-dried and milled according to Yan et al. (2019), then dry acid pretreated (Zhang et al., 2011). The pretreated corn stover contained 37.6 % of cellulose and 4.4 % of hemicellulose determined by the NREL LAP protocols (Sluiter et al., 2008a, b). The pretreated corn stover was then biodetoxified by *A. resinae* ZN1 to remove the inhibitors (He et al., 2016; Zhang et al., 2010). After biodetoxification, acetic acid, furfural, HMF and phenolic aldehydes were removed completely, but 0.09 mg/g DM (dry matter) of *p*-benzoquinone was remained.

Simultaneous saccharification and D-lactic acid co-fermentation (SSCF) was conducted in a 5 L helical agitated bioreactor according to Qiu et al., 2017. The feedstock used was 30 % (w/w) solids loading of the pretreated and biodetoxified corn stover. The dosage of the cellulase Cellic CTec 2.0 was 10 mg protein/g cellulose. The SSCF was carried out at 42 °C, 150 rpm for 72 h with pH at 5.5 controlled by automatically adding 25 % (w/w) $Ca(OH)_2$ slurry. 34.0 mg/L of *p*-benzoquinone was detected in the SSCF broth.

2.6. HPLC analysis

Quantification of glucose, xylose and D-lactic acid were carried out by HPLC (LC-20AD, Shimadzu, Kyoto, Japan) with an Aminex HPX-87H column (Bio-Rad, Hercules, CA, USA) according to the method described in Qiu et al., 2018.

Analysis of *p*-benzoquinone and hydroquinone were performed using HPLC (LC-20AT; Shimadzu, Kyoto, Japan) with an SPD-20A detector and a YMC-Pack ODS-A column (YMC, Tokyo, Japan) (Yan et al., 2019).

3. Results and discussion

3.1. Construction of p-benzoquinone conversion pathway in P. acidilactici

To release the toxicity of *p*-benzoquinone to *P. acidilactici* ZY15, we constructed the *p*-benzoquinone conversion pathway in *P. acidilactici* to reduce *p*-benzoquinone into the less toxic hydroquinone (Fig. 1). Five oxidoreductase genes were selected from the high *p*-benzoquinone tolerant *Z. mobilis* ZM4, including an oxidoreductase gene *ZMO1116*, a fatty acid hydroxylase *gene ZMO1399*, a short chain dehydrogenase/reductase gene *ZMO1576*, a zinc-binding alcohol dehydrogenase gene *ZMO1696*, and an aldo-keto reductase gene *ZMO1984* (Yan et al., 2019). The five oxidoreductase genes were inserted into the plasmid pZY36e under the control of promoter *PldhD* and then introduced into

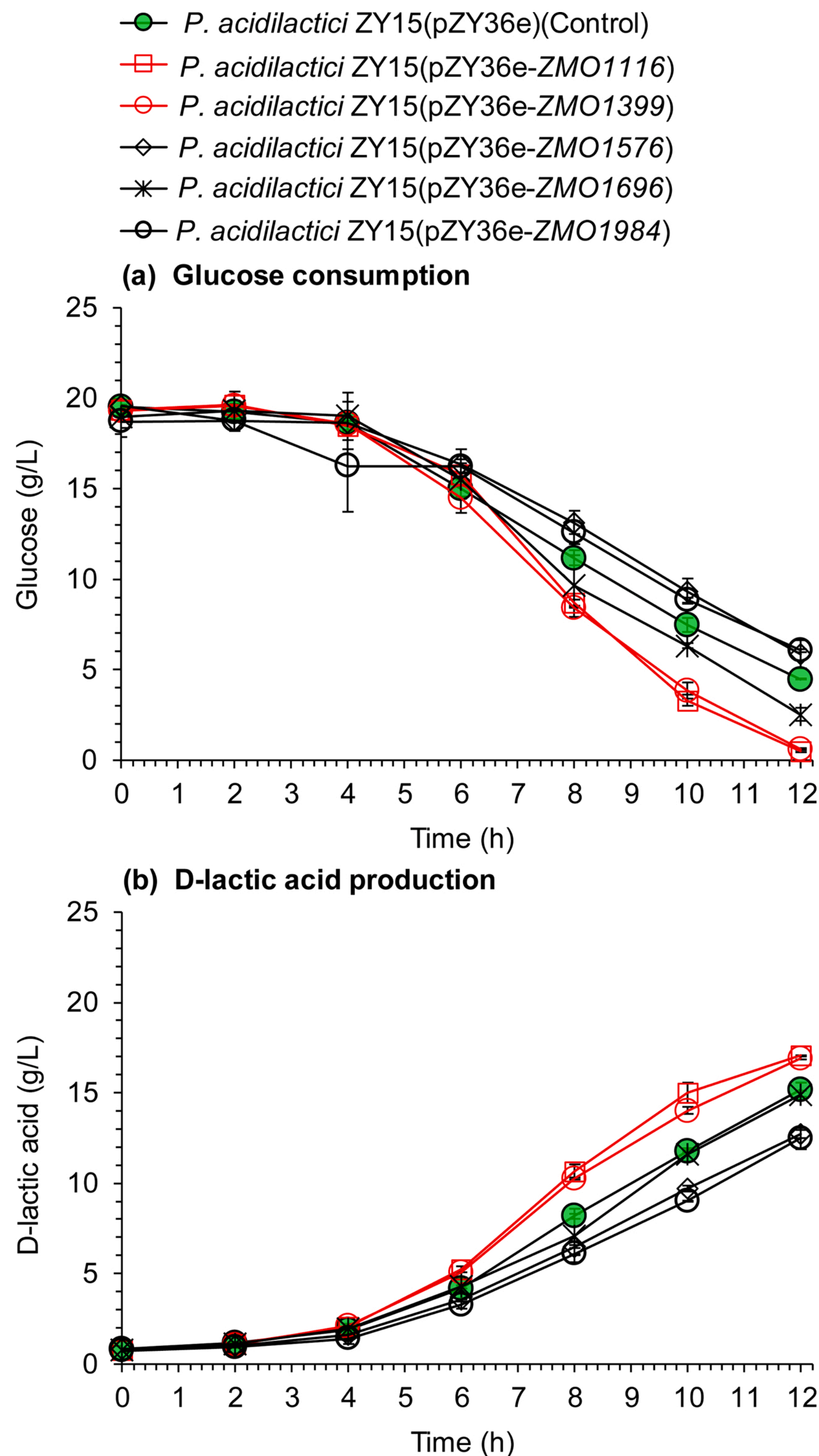

Fig. 2. Fermentation evaluation of *P. acidilactici* ZY15 recombinants under *p*-benzoquinone stress. Fermentation conditions: 50 mL of MRS medium containing 50 mg/L of *p*-benzoquinone in 250 mL shaking flasks with 5 μg/mL of erythromycin addition, 10 % (v/v) inoculate size, 42 °C, 150 rpm for 12 h. pH was controlled by adding 0.6 g $CaCO_3$ per gram glucose.

P. acidilactici. The recombinants were evaluated in the *p*-benzoquinone (50 mg/L) containing MRS medium (Fig. 2). The results show that the overexpression of genes *ZMO1116* and *ZMO1399* led to the increases of glucose consumption by 25.2 % and 23.8 % and D-lactic acid production by 14.0 % and 13.3 %, respectively, compared with the control strain. The overexpression of the genes *ZMO1576*, *ZMO1696* and *ZMO1984* did not show any observable improvements in D-lactic acid fermentation.

To obtain the stable *p*-benzoquinone tolerant strains, the genes *ZMO1116* and *ZMO1399* were separately integrated into the *ackA2* locus of *P. acidilactici* genome by thermo-sensitive homologous recombination (Yi et al., 2016). Two engineered strains *P. acidilactici* ZY15-Δ*ackA2*::*ZMO1116* and *P. acidilactici* ZY15-Δ*ackA2*::*ZMO1399* were obtained. The two engineered strains were then adaptively evolved for 90 days to stabilize the expression of the integrated heterologous gene. However,

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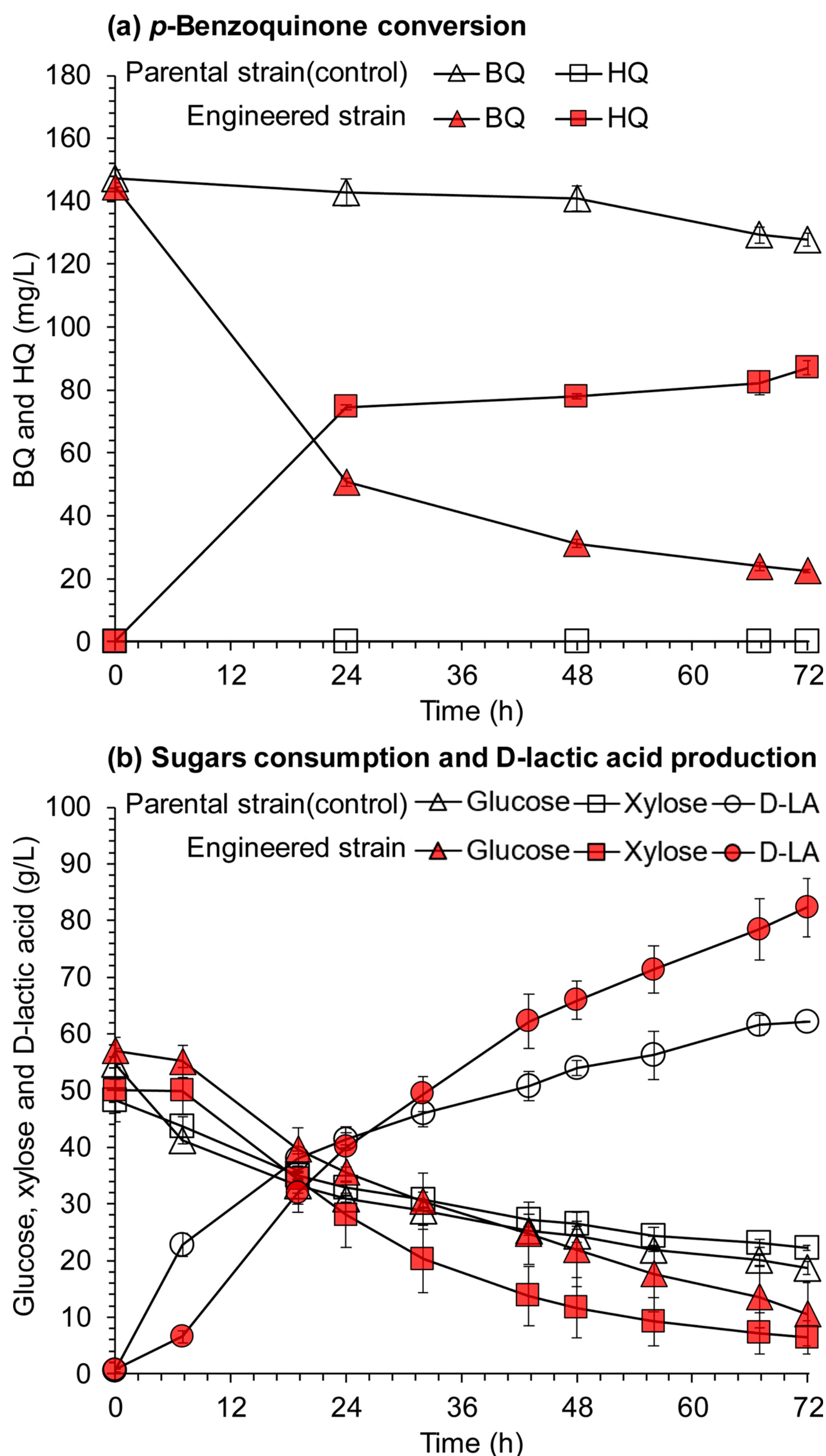

Fig. 3. *p*-Benzoquinone conversion and D-lactic acid fermentability of the engineered strain *P. acidilactici* ZY15-Δ*ackA2*::*ZMO1116*. (a) *p*-Benzoquinone conversion; (b) Sugars consumption and D-lactic acid production. The medium contained 60 g/L glucose, 50 g/L xylose, and 150 mg/L *p*-benzoquinone (BQ). The fermentation was conducted in a 1 L bioreactor with 600 mL of MRS medium, at 42 °C, 150 rpm, 10 % (v/v) inoculate size. pH was controlled at 5.5 by automatically adding 25 % (w/w) $Ca(OH)_2$ slurry. The parental strain *P. acidilactici* ZY15 was used as control.

one of the two strains, *P. acidilactici* ZY15-Δ*ackA2*::*ZMO1399*, was found that the D-lactic acid fermentability was reduced (data not shown). Therefore, only *P. acidilactici* ZY15-Δ*ackA2*::*ZMO1116* was chosen for the late stage fermentation applications.

3.2. p-benzoquinone conversion and lactic acid fermentability of the engineered P. acidilactici

The *p*-benzoquinone conversion and D-lactic acid fermentability of the engineered *P. acidilactici* ZY15-Δ*ackA2*::*ZMO1116* was evaluated in the MRS medium containing 60 g/L glucose, 50 g/L xylose, and 150 mg/L of *p*-benzoquinone (Fig. 3). Fig. 3a shows that about 85 % of *p*-benzoquinone (122 mg/L) was converted to hydroquinone (87 mg/L) during 72 h, while no observable conversion of *p*-benzoquinone to hydroquinone was found for the parental strain. Glucose and xylose consumption, as well as D-lactic acid generation increased by 29.2 %, 66.8 %, and 32.5 % higher than that of the parental strain, respectively (Fig. 3b). However, the D-lactic acid fermentability of the engineered strain was lower than that of the parental strain in the early phase (0−24 h) then increased afterwards (Fig. 3b). This was probably due to the

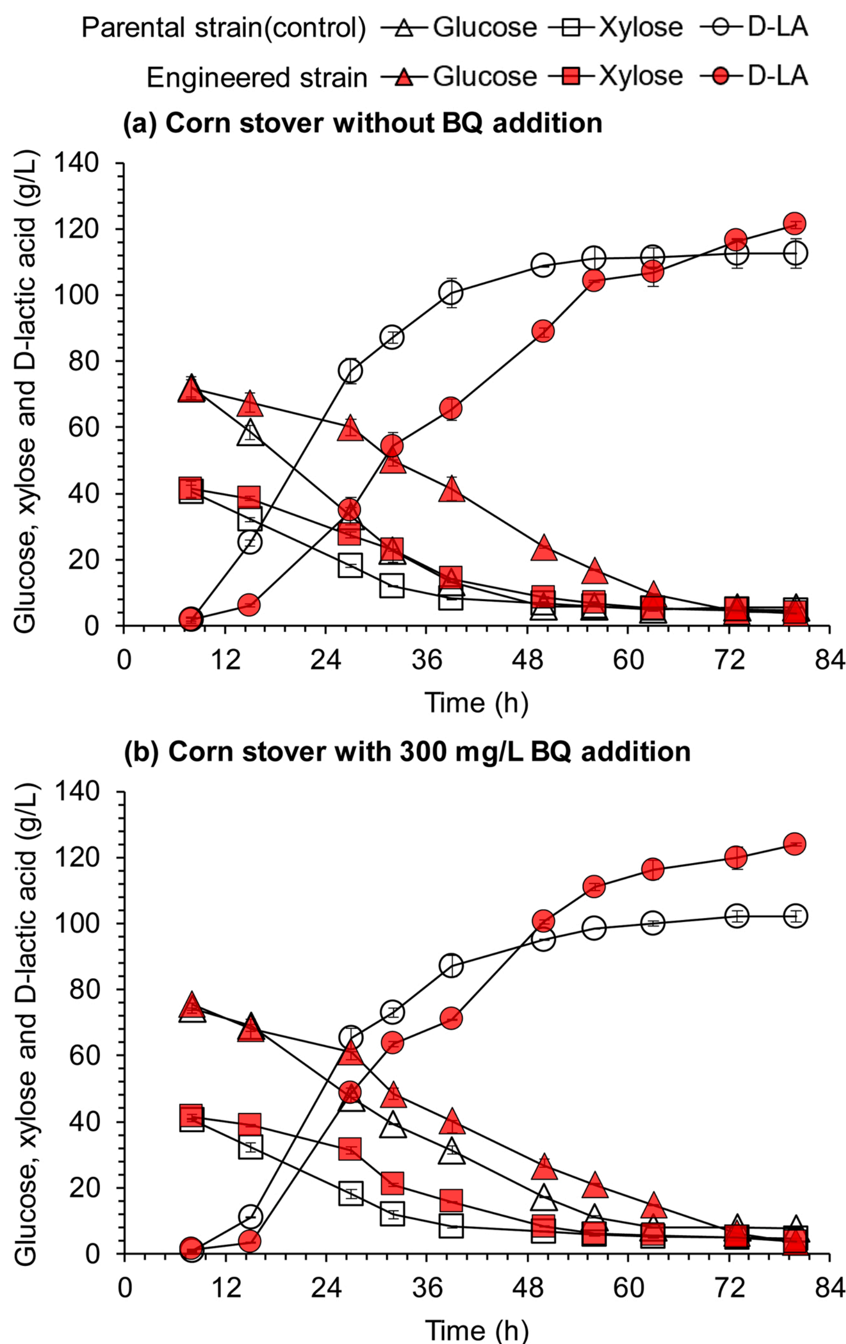

Fig. 4. Simultaneous saccharification and co-fermentation (SSCF) of D-lactic acid by the engineered strain *P. acidilactici* ZY15-Δ*ackA2*::*ZMO1116*. (a) Corn stover without BQ addition; (b) Corn stover with 300 mg/L BQ addition. The SSCF was conducted using the 30 % (w/w) solids loading of dry acid pretreated and biodetoxified corn stover, 10 mg cellulase protein per gram cellulose. 34 mg/L *p*-benzoquinone (BQ) was detected in the SSCF broth. pH was maintained at 5.5 by automatic feeding of a 25 % (w/w) $Ca(OH)_2$ slurry. The parental strain *P. acidilactici* ZY15 was used as control.

competing consumption of NADH and/or NADPH cofactor(s) for reductive conversion of *p*-benzoquinone to hydroquinone. With the decreased toxic *p*-benzoquinone content in the medium, the D-lactic acid fermentability was improved.

The simultaneous saccharification and D-lactic acid co-fermentation (SSCF) was conducted to evaluate the cellulosic D-lactic acid fermentation using dry acid pretreated and biodetoxified corn stover (Fig. 4). The *p*-benzoquinone concentration was only 34 mg/L which poorly inhibited the parental strain, and the D-lactic acid production of the engineered strain just slightly increased (7.6 %) than that of the parental in the SSCF broth. To demonstrate the strong *p*-benzoquinone tolerance of the engineered strain, more *p*-benzoquinone (300 mg/L) was added into the SSCF broth (totally containing 334 mg/L), the cellulosic D-lactic acid production of the engineered strain (123.8 g/L) was apparently increased by 21.4 % than the parental strain (102.0 g/L) (Fig. 4b).

p-Benzoquinone is a lignin-derived aldehyde inhibitor and difficult to be completely removed by various detoxification methods when fermentable sugars were retained in the pretreated lignocellulose feedstock (Yan et al., 2019). This study demonstrated a practical solution of realizing *p*-benzoquinone conversion to its less toxic alcohol-derivative hydroquinone by using the engineered fermentation strain cells during the fermentation period. We successfully constructed the *p*-benzoquinone reduction conversion pathway in *P. acidilactici* by genome integration of gene *ZMO1116* encoding oxidoreductase from *Z. mobilis*. The toxic *p*-benzoquinone inside the cells was converted into less toxic hydroquinone by the recombinant cells, the inhibition of *p*-benzoquinone to strain was weakened and the tolerance to *p*-benzoquinone was therefore improved. Consequently, the cellulosic D-lactic acid fermentability from corn stover containing *p*-benzoquinone was enhanced. Future works should focus on the NAD(P)H regeneration by

overexpressing genes such as glucose-6-phosphate dehydrogenase, isocitrate dehydrogenase and/or malic enzyme (Sauer et al., 2004; Hua et al., 2003; Spaans et al., 2015), to further enhance the D-lactic acid fermentability of *P. acidilactici* against *p*-benzoquinone.

4. Conclusion

p-Benzoquinone is a toxic lignin-derived inhibitor to *P. acidilactici*. The reduction conversion pathway of *p*-benzoquinone into less toxic hydroquinone was successfully constructed in *P. acidilactici* by genome-integrating a heterologous gene *ZMO1116* encoding oxidoreductase from *Z. mobilis* ZM4, resulting in the improved *p*-benzoquinone tolerance of *P. acidilactici*. Consequently, the D-lactic acid production by SSCF of the engineered strain (123.8 g/L) was 21.4 % higher than the parental strain (102.0 g/L) from the dry acid pretreated and biodetoxified corn stover with *p*-benzoquinone contained.

Author contributions section

JB conceived of the study. CF and ZYQ conducted the metabolic engineering experiments, the assay and the fermentation experiments. NLH partially participated the fermentation experiment and helped the analysis. ZYQ and JB wrote the manuscript. CF partially participated the writing of the manuscript. All authors approved the manuscript.

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.

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