Statistical Optimization of Itaconic Acid Fermentation from Oil Palm Empty Fruit Bunch by *Aspergillus terreus* K17 for the Application in Textile Industry

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ABSTRACT

Itaconic acid (IA) is an important building block chemical, widely applied in textile, chemical and pharmaceutical industries. The effects of solid loading and ammonium nitrate (Na_2CO_3) concentration on IA fermentation from oil palm empty fruit bunch (OPEFB) were evaluated through response surface methodology (RSM) based on central composite design (CCD). OPEFB was pretreated by steam explosion and then converted into fermentable sugars by enzymatic hydrolysis. The fermentation was carried out through a separate hydrolysis and fermentation (SHF) process by *Aspergillus terreus* K17. Solid loading and ammonium nitrate concentration clearly affected IA production. IA concentration increased as solid loading and ammonium nitrate concentration increased but began to decline after solid loading and ammonium nitrate concentration reached 160 g/L and 0.03 g/L, respectively. The maximum observed value of IA concentration at 7.43 g/L corresponding with a predicted value at 7.12 g/L was obtained from the optimized medium composition (150 g/L of solid loading and 0.03 g/L of ammonium nitrate concentration). The optimized value was scaled-up toa 3-L air-lift fermenter, temperature 30°C, pH 2.5 and aeration rate 2.0 yielded the highest itaconic acid concentration of 30.45 g/L at 72 h with a yield and productivity of 0.51 g/g and 0.42 g/L/h, respectively.

Keywords: Itaconic acid, oil palm empty fruit bunch, separate hydrolysis fermentation (SHF), response surface methodology (RSM)

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INTRODUCTION

Itaconic acid (IA) or 2-methylidenebutanedioic acid, is an unsaturated di-carboxylic acid (Wilke and Vorlop, 2001), which is an important building block chemical. It is widely used in textile, chemical and pharmaceutical industries (El-Imam and Du, 2014) as in the synthesis of fiber, resin, plastic, rubber, paints, surfactant, ion-exchange resins and lubricant (Milson and Meers, 1985). Since the 1960s, IA has been produced from sugar containing media by *Aspergillus terreus* (Willke and Vorlop, 2001). IA can also be produced by other microorganisms including *Ustilagozeae* (Haskins *et al.*, 1955), *Ustilago maydis*, *Candida* sp. (Tabuchi *et al.*,1981), and *Rhodotorula* sp. (Kawamura *et al.*, 1981), however, *A. terreus* is still the dominant species due to it can reach the highest IA production (Okabe *et al.*,

2009; Kuenz *et al.*, 2012). In 2013, the capacity of IA production worldwide was reported to be higher (50,000 MT per year) than its demand (30,000 MT per year) (Steiger *et al.*, 2013). However, growing use of super-absorbent polymers, synthetic rubber, poly-IA and unsaturated polyester resins provides opportunities for the global market growth of IA. IA production using renewable feedstocks as substrate is then expected to approximately 407,790 MT by 2020 (Weastra, 2018).

Currently, Thailand is in the top five palm oil producing countries, ranking the third place after Indonesia and Malaysia (Gerard, 2017). Oil palm empty fruit bunch (OPEFB) is an agricultural residue from palm oil industry, located in large quantities in Southern Thailand. A palm oil extraction process yields huge amount of biomass residues, especially OPEFB, accounting 20% of the fresh fruit weight (Mohammad *et al.,* 2012). Approximately 2 MMT of OPEFB are generated each year in Thailand. The OPEFB consists of around 65.5% holocellulose, which is rather high and very promising feedstocks for production of bio-based materials (Faharna, 2010).

This research aims to evaluate the efficiency of OPEFB as a cellulosic substrate for IA production by *A. terreus* K17, as well as to investigate the optimum levels of factors including solid loading and ammonium nitrate for IA production.

MATERIALS AND METHODS

Microorganisms and Culture Conditions

The filamentous fungi used in this research, was isolated from soil samples from Nakhon Ratchasima Province in Thailand and grown on PDA agar plate containing (g/L) potato, 200; glucose, 20; and agar, 15 with final pH 5.6. It has been genetically identified as *Aspergillus terreus* K17. A spore suspension of 1×10^7 spores/ml was inoculated into 100 ml of growth medium containing (g/L) glucose, 60; KH_2PO_4, 0.88; $MgSO_4 \cdot 7H_2O$, 0.95; NH_4NO_3, 4; and $CuSO_4$, 0.004; in 250-ml Erlenmeyer flask and incubated at 30°C for 24 h on a rotary shaker at 150 rpm for seed culture preparation. A polyurethane foam cube ($0.5 \times 0.5 \times 0.5$ cm^3) was prepared for immobilized device and put into 250 ml Erlenmeyer flask. The seed culture was transferred to each flask containing 100 ml of growth medium and incubated at 30°C for 24 h on a rotary shaker at 150 rpm. After that, the immobilized device was washed twice with sterile water and transferred into production medium containing same components as the growth medium except KH_2PO_4 ((g/L) glucose, 60; $MgSO_4 \cdot 7H_2O$, 0.95; NH_4NO_3, 4; and $CuSO_4$, 0.004), which was operated at 30°C for 96 h on a rotary shaker at 150 rpm. The pH value was adjusted to 3.1 with 1 M H_2SO_4 before autoclaving. Phosphate (KH_2PO_4) is a basic component required for the production of phospholipids present in the microbial cell membranes, thus it was added in the growth medium to obtain high cell contents (Singh *et al.*, 2017). The IA fermentation process, however, worked best under phosphate-limited conditions, thus KH_2PO_4 was removed in order to improve the IA production (Karaffa and Kubicek, 2019).

Raw Material

Oil palm empty fruit bunch (OPEFB) was obtained from the Suksomboon Palm Oil Industry in Chonburi Province, Thailand. They were dried, chopped to a particle size of approximately 2.5 cm and kept in a sealed plastic bag until use. The chemical compositions of OPEFB were determined according to standard TAPPI (Technical Association of Pulp and Paper Industry) methods: T204 om-88 (1997) for extractives; T222 om-88 (1988) for Klason (acid-insoluble) lignin; and T203 om-88 (1992) for α-cellulose. The holocellulose content was determined according to Browning 1967.

Pretreatment of Raw Material

Approximately 200 g of OPEFB were steam-exploded at 20 MPa (210°C) for 4 min in a 2.5-L stainless steel batch digester (NittoKoatsu Co. Ltd., Tokyo, Japan). The material was then separated into a solid residue and liquid. The solid residue was cleaned by soaking in hot water at 80°C for 60 min, and washed with tap water until it reached a neutral pH. It was then used for further delignification in a 15% (w/v) sodium hydroxide (NaOH) solution at 90°C for 30 min. After that, the

solid residues were washed with tap water until it reached a neutral pH. The delignified solid was dried at 60°C in an oven and stored in a sealed plastic bag for further experiment.

Separate Hydrolysis and Fermentation (SHF) Process of Itaconic Acid

The production of itaconic acid (IA) was carried out using the delignified OPEFB as substrate through a separate hydrolysis and fermentation (SHF) process. Enzymatic hydrolysis was performed using a CellicCTec 2 (185 FPU/mL, Novozyme A/S, Basgsværd, Denmark) in a citrate buffer (50 mM, pH of 4.8) at 50°C with 150 rpm for 24 h. The enzyme loading was fixed at 15 FPU/g raw material. After saccharification, the produced glucose for 150 g solid loading was 60 g. The Nelson-Somogyi method (Somogyi, 1952) was used to determine the released sugar concentration. IA fermentation was operated in a 250 mL Erlenmeyer flask containing 100 ml of production medium, the seed culture, except that the enzymatic hydrolysate was used in place of glucose at 30°C for 168 h on a rotary shaker at 150 rpm. Aliquots of the samples were taken every 24 h for IA concentration determination. IA concentration was measured by High Performance Liquid Chromatography (HPLC; CTO-20A, Shimadzu Co. Ltd., Kyoto, Japan) using a Bio-Rad (Richmond, USA) aminex HPX-87H column (300 mm × 7.8 mm) at 60°C, with 0.005 N of sulfuric as a mobile phase, a flow rate of 1 mL/min, and a pressure of 100 kgf/cm^2. Samples were filtered through 0.25 µm filter previous to the HPLC analysis. Standard solution of IA with 99% purity (Sigma–Aldrich, St. Louis, MO) was prepared at authentic quantify.

Experimental Design

Optimization of agitation speed

To determine the effect of the agitation speed on IA production, the fermentation was varied at 0 rpm (static condition), 50 rpm, 100 rpm, 200 rpm, and 250 rpm through a SHF process as mentioned above. Aliquots of the samples were taken every 24 h for 96 h for IA concentration determination. Optimization of solid loading and ammonium nitrate concentration.

Table 1 Experimental codes, ranges and levels of the independent variables for response surface methodological experiment

Variable	Parameter (g/L)	Levels				
		-1.414	-1	0	+1	+1.414
X_1	Solid loading	79.30	100	150	200	220.70
X_2	Ammonium nitrate concentration	0.01	0.02	0.03	0.04	0.05

Response surface methodology (RSM) based on central composite design (CCD) was used to evaluated the parameters and response data. The variable factors, solid loading (79.3 to 220.7 g/L) and ammonium nitrate concentration (0.01 to 0.05) with five for each (Table 1). A total of 11 runs were conducted. Dwiarti *et al.* (2007) reported the effect of both factors, substrate concentration and ammonium nitrate concentration on IA production. As well as Pfeifer *et al.* (1952) found that the addition of nitrogen source, especially ammonium nitrate, was very important for IA production. Therefore, both factors were selected for optimization. A full factorial design with four-star points and three replicates at the center point resulting in a total of 11 runs were used to optimize the factors for

IA concentration in shake flask culture (Table 2). For predicting the optimal value, a second-order polynomial equation was established as equation 1 to correlate the relationship between variables and response. The equation is

$$Y = a_0 + a_1X_1 + a_2X_2 + a_{11}X_1^2 + a_{22}X_2^2 + a_{12}X_1X_2 \quad (1)$$

where Y is the predicted response (IA concentration, g/L); a_0 is a constant term; a_1 and a_2 are linear terms; a_{11} and a_{22} are quadratic terms; a_{12} is an interaction term and X_1 and X_2 are test variables studied.

The statistical software package, Design Expert software (Stat Ease, Version 7.0, Minneapolis, MN, USA) was used to evaluate the analysis of variance (ANOVA) and draw the response surface graphs. Subsequently, a validity of the model was carried out to yield the maximum response of each variable and confirm the results from an analysis of the response surface method.

Batch fermentation in an airlift fermenter

The optimized values obtained from CCD, was performed in a 3-L air-lift fermenter (Model: MCI-6C, B.E. Marubishi Co., Ltd., Bangkok, Thailand) containing 1 L of the production medium. IA production was carried out at different temperature, including 25°C, 30°C and 35°C. To determine the effect of initial pH of IA production, the experiment was done at different pH, including 2.5, 3.0 and 3.5. As well as the aeration rate was varied at 1.5, 2.0 and 2.5 vvm. The samples were taken every 24 h for 120 h and IA concentration was determined by HPLC as described above.

RESULTS AND DISCUSSION

Pretreatment of Raw Material

The cellulose content of OPEFB raw material was 65.48% and increased to 75.25% based on dry weight after steam explosion pretreatment, whereas the hemicellulose, lignin and extractive in ethanol/benzene contents decreased to 2.02%, 7.50%, and 2.11% from 22.19%, 15.18% and 3.21%, respectively. Under high temperature and high pressure of steam explosion process, acetic acid from acetyl groups of the materials was released by the autohydrolysis. After that, an explosive decompression occurred by reducing pressure suddenly was able to separate the biomass to each other, degrade lignin and hemicellulose, and thus increase the potential of cellulose hydrolysis. The OPEFB showed sufficiently high cellulose content compared to softwood, hardwood (McKendry, 2002), bamboo (Sánchez, 2009), corncobs (Kuhad and Singh, 1993; Prasad *et al.*, 2007; Liu *et al.*, 2010), and switch grass (Butkute *et al.*, 2013; Saini *et al.*, 2015). This relative high content of cellulose obtained from OPEFB can be useful for fermentable sugars preparation in the bioconversion processes.

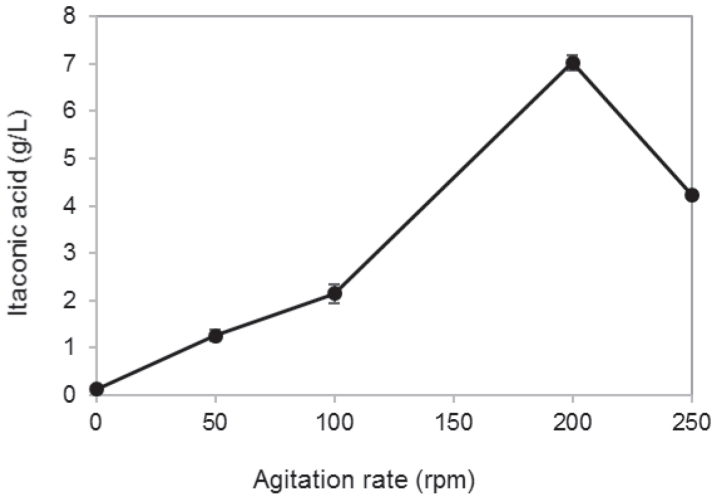

Figure 1 Effect of agitation rate (0, 50, 100, 200 and 250 rpm) on IA production for 96 h cultivation through a SHF process

Optimization of Agitation Speed

The effect of agitation speed on IA production by *A. terreus* K17 was varied at 0 rpm (static condition), 50 rpm, 120 rpm, 200 rpm and 250 rpm. According to Figure 1, at agitation speed of 200 rpm, the IA concentration reached the highest IA concentration at 7.02 g/L after 96 h cultivation. This result was in correspondence with the report obtained from Meena *et al.* (2010). They found that agitation speed obviously affected IA production by the four selected microbial fungal species including *A. niger*, *A. terreus*, *A. nidulans* and *A. flavus.* The maximum IA concentration was achieved at 200 rpm in all selected species. IA concentration was slightly decreased with the increase in rpm from 200 to 250. The effect of agitation speed or aeration rate on IA production was also reported by Klement and Büchs (2013) and Boruta and Bizukojc (2017). The growth of *A. terreus* and biosynthesis of IA required a sufficient oxygen supply, which was provided from an optimal agitation speed or aeration rate. At higher speed the product production was rather low due to the impact of mechanical shear stress. On the other hand, insufficient agitation speed or aeration rate caused product formation interference due to the cessation of oxygen supply (Klement and Büchs, 2013; El-Imam and Du, 2014; Boruta and Bizukojc, 2017). Gao *et al.* (2014) reported that the efficiency of IA production could be affected by fungal pellet morphology. The pellet formation could be controlled by the growth conditions including agitation rate, pH, temperature, and so on. Any changes in the agitation rate affected pellet morphology which then resulted in decreasing or increasing of IA concentration. However, the optimum agitation speed or aeration rate needs to be optimized at the individual microorganisms.

Table 2 The effects of process factors including solid loading and ammonium nitrate on the IA concentration during the fermentation of OPEFB obtained by experimental design

Run no.	Level		Actual level		IA concentration (g/L)	
	X_1	X_2	X_1 (solid loading, g/L)	X_2(NH_4NO_3, g/L)	Observed	Predicted
1	-1	-1	100	0.02	4.20	4.21
2	1	-1	200	0.02	5.34	5.17
3	-1	1	100	0.04	5.34	4.77
4	1	1	200	0.04	4.83	4.89
5	-1.414	0	7.93	0.03	4.68	3.53
6	1.414	0	220.70	0.03	5.18	4.44
7	0	-1.414	150	0.02	4.42	3.53
8	0	1.414	150	0.04	4.94	3.76
9	0	0	150	0.03	7.12	7.06
10	0	0	150	0.03	7.09	7.06
11	0	0	150	0.03	7.16	7.06

Optimization of Solid Loading and Ammonium Nitrate Concentration

To identify the optimal independent factors (solid loading and ammonium nitrate concentration) on IA production, RSM based on CCD were investigated. The level of each factor with the coded level and IA concentration are given in Table 2. Analysis of variance (ANOVA) for the determination of significant parameters is shown in Table 3. The regression based determination coefficient R^2 (0.9972) suggested that 99.72% of the variability in the response could be explained. When considering Fisher's *F*-test with a very low probability value (*P*-model >*F* = 0.0001) the model was highly significant. This implied a satisfying representation of the response equation provided a suitable model of the relationship between the independent variables and the response. The model equation for IA production can be expressed as follows:

$$Y = 7.06 + 0.27X_1 + 0.071X_2 - 0.21X_1X_2 - 1.09X_1^2 - 1.21X_2^2 \quad (2)$$

Where Y is IA concentration (g/L), X_1 is solid loading (g/L), and X_2 is ammonium nitrate concentration (g/L)

Table 3 Analysis of variance (ANOVA) for the fitted quadratic polynomial model for optimization of IA concentration

Source	Sum of Squares	DF	Mean Square	F	P-value
Model	12.31	5	2.46	355.81	<0.0001*
X_1	0.22	1	0.22	32.29	0.0024*
X_2	0.23	1	0.23	33.67	0.0021*
X_1X_2	0.68	1	0.68	98.33	0.0002*
X_1^2	6.42	1	6.42	927.11	<0.0001*
X_2^2	8.01	1	8.01	1157.27	<0.0001*
Residual	0.035	5	6.922E-003		
Lack of fit	0.032	3	0.011	8.69	0.1050
Total	12.35	10			

Note: R^2 = 0.9972, Adjusted-R^2 = 0.9944, * = Significant at P < 0.05

Table 3 shows the model coefficients estimated by regression analysis for each variable. The significant of each coefficient used to explain the interaction between the variables was determined by P-value. The results demonstrated that both of independent variables, solid loading (X_1) and ammonium nitrate concentration (X_2) significantly affected IA production. The interactions between solid loading and ammonium nitrate concentration (X_1X_2), the quadratic term of solid loading (X_1^2), and ammonium nitrate concentration (X_2^2) were significant (Table 3).

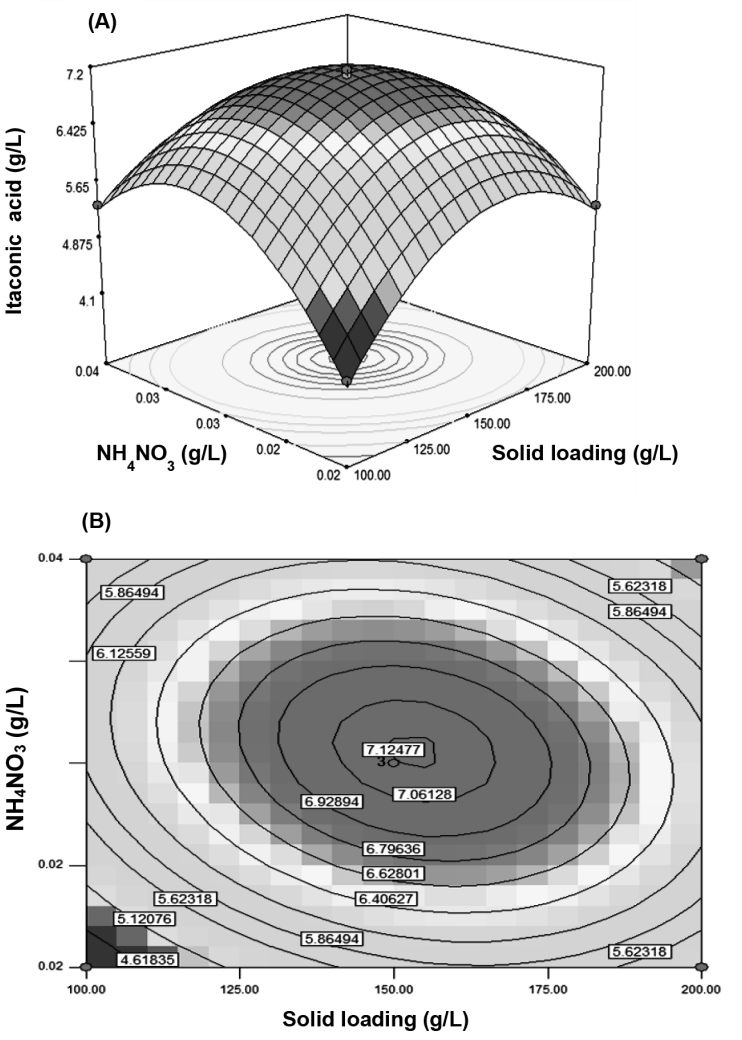

Figure 2 Response surface (A) and contour plots (B) of two factors (solid loading and ammonium nitrate) on IA production by *A. terreus* K17

The interaction of the independent variables and the optimum levels affected IA production was evaluated by the 3D response surface plot and 2D contour plot (Figure 2). This figure indicated the significant interaction between the corresponding variables on IA concentration. When solid loading increased the IA concentration increased, but began to decline after the solid loading reached 160 g/L. Likewise, the IA concentration increased with the increasing of ammonium nitrate concentration up to 0.03 g/L, after this range the IA concentration began to decline.

The regression equation and response surface contour plots obtained from Design Expert software were used to determine the optimal values of the variables. The prediction of the maximum IA concentration from the model was 7.12 g/L at 150 g/L of solid loading and 0.03 g/L of ammonium nitrate concentration. Verification of the predicted model was repeated three times under optimum

condition. The observed value was 7.43 g/L which corroborated the validity of the response model and the existence of an optimum point. This was in agreement with the observation of Dwiarti *et al.* (2007), who reported the optimized values of substrate concentration (sago starch) and ammonium nitrate concentration on IA production. Both factors had a significant effect on IA production. Increasing of IA production could be achieved with the increase of sago starch concentration and ammonium nitrate concentration. The optimized medium contained 140 g/L sago starch and 2.9 g/L ammonium nitrate with other compositions reached the highest yield of 0.36 g/g. IA production from other biomass hydrolysates has also been investigated. Jiménez-Quero (2016) studied IA production using liquid-state fermentation (LSF) obtained from wheat bran and corn cobs by *Aspergillus* strains. Wheat bran and corn cobs were pretreated by dilute acid and enzymatic cocktail for hydrolysates preparation. The maximum yield and concentration of IA were 0.5 g IA/g total glucose and 90 g/L, respectively, which obtained by LSF of corn cob hydrolysate by *A. oryzae*. These results indicated that both solid loading and ammonium nitrate concentration obviously affected IA production, which could be produced from hydrolysate of lignocellulosic materials.

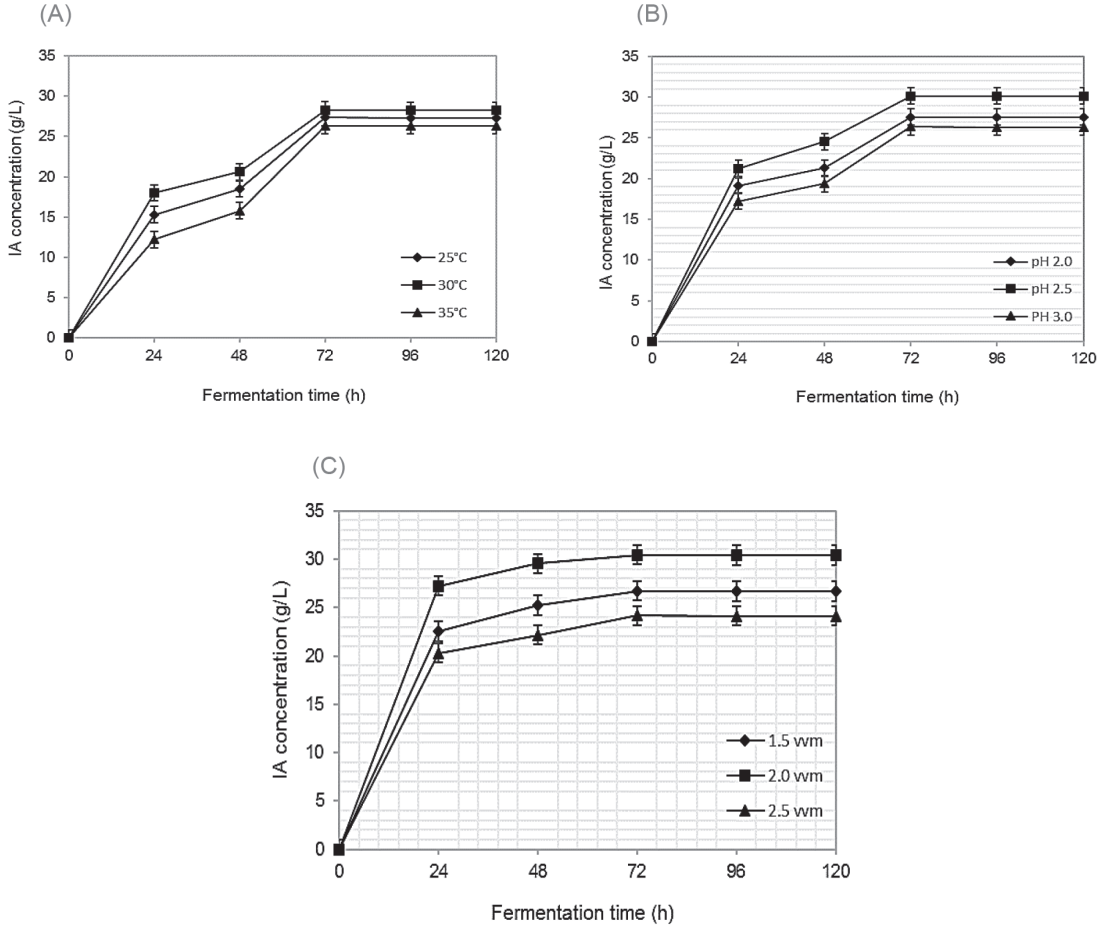

Figure 3 Time course of batch fermentation for IA production from isolate *A. terreus* K17 under optimized conditions at various (A) temperatures, (B) initial pH and, (C) aeration rates

Batch Fermentation in an Airlift Fermenter

The optimized values obtained from flask scale was upscale by batch fermentation in a 3-L air-lift fermenter (Model: MCI-6C, B.E. Marubishi Co., Ltd., Bangkok, Thailand) with a working volume of 1 L. The maximum concentration, productivity and yield were 30.45 g/L, 0.42 g/L/h and 0.51 g/g glucose, respectively, within 72 h at temperature of 30°C, initial pH of 2.5 and aeration rate of 2.0 vvm. The optimum temperature, initial pH and aeration rate are shown in Figure 3. The yield production from air-lift fermenter was higher than that from flask scale cultivation (0.51 g/g glucose versus 0.098 g/g glucose). IA production in term of concentration, yield and productivity in air-lift fermenter were higher than that in shake flask. This could be due to the better mixing, suitable gas hold-up and liquid circulation velocity (Kang *et al.*, 2001). This research was in accordance with report of Yahiro *et al.* (1995), who produced IA in air-lift fermenter with working volume of 2.5 L containing the optimum condition obtained from flask scale. The air-lift fermentation resulted in higher concentration of IA (72.5 g/L at 144 h) when compared with the flask scale. Similarly, Xiaoxian *et al.* (2012) and Hajian *et al.* (2017) found that IA production was affected by temperature and initial pH. The optimum values of temperature and initial pH were in the range of 30–37°C and 2.4–2.6, respectively, which corresponded with those values obtained from our research.

CONCLUSION

Based on this research, *A. terreus* K17 is an effective IA producer that can consume hydrolysate from lignocellulosic materials including OPEFB. The use of OPEFB as feedstocks, can create a value-added product, eliminate residues from communities and industrial factories, and also prevent environmental pollution. Scale up of the production in bioreactor fermenter improved the productivity and yield of IA production. Moreover, improvement in IA recovery and purification will be done and applied in anti-crease finishing of cotton for future prospective.

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