OPTIMISATION AND KINETIC MODELLING FOR THE PRODUCTION OF 5-AMINOLEVULINIC ACID BY *RHODOPSEUDOMONAS PALUSTRIS* IN THE SOLID STATE FERMENTATION

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DEDICATION

To my beloved family for their love and support

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ABSTRACT

The approach of the bioprocess system engineering (BPSE) serves as a systematic methodology to better understand the overall performance of complex biological system through optimisation process and development of a compatible macroscopic kinetic model. Based on the BPSE approach, the production of 5-aminolevulinic acids (ALA) by *Rhodopseudomonas palustris* (*Rp*) via solid state fermentation (SSF), using the palm empty fruit bunch as solid state medium was studied. Optimisation studies were carried out using a full-factorial design and the response surface methodology approach. A maximum ALA yield of 43.72 mg/kg was achieved under the following optimum conditions: moisture content of 63.13 %, incubation temperature of 30.3 ℃, pH 7, inoculums density of 40 % (v/w), 3.64 mM glycine and 23.03 mM succinic acid for 48 hours via SSF. Three mathematical models including the Logistic, Gompertz and Luedeking-Piret models were proposed and compared based on their goodness of curve-fitting to the SSF experimental data. The Logistic model incorporated with Luedeking-Piret model was developed and best represented (R^2 >0.95) the underlying kinetic behaviour of the growth of *Rp*, the formation of ALA and the consumption of substrates for the production of ALA by *Rp* in SSF at the optimum condition. The computed kinetic parameters including the maximum specific growth rate (μ_m= 0.232 h^{-1}) with the maximum *Rp* biomass concentration (X_{max}= 316.4 x 10^{-9} CFU.g^{-1}) for the modelling of *Rp* growth; the growth-associated (α= 8.249 mg.kg^{-1}.h^{-1}) and non-growth associated (β = -1.660 mg.kg^{-1}.h^{-1}) coefficients for the modelling of ALA formation, and the *Rp* growth associated and the ALA formation associated on substrate consumption coefficient ($Y_{X/S}$ = 0.132 and $Y_{P/S}$ = 0.141) for the modelling of substrate consumption were evaluated. These values were then validated between the predicted data and the experimental data using the least square curve fitting analysis and the ordinary differential equation solver (ODE45) using the Matlab software.

ABSTRAK

Sistem kejuruteraan bioproses (BPSE) menyediakan metodologi yang sistematik untuk lebih memahami prestasi keseluruhan dalam sistem biologi yang kompleks melalui pengoptimuman dan pembentukan model kinetik makroskopik yang sesuai. Berdasarkan kaedah sistem BPSE, penghasilan asid aminolevulinik (ALA) daripada *Rhodopseudomonas palustris* (*Rp*) melalui proses fermentasi pepejal (SSF) dengan menggunakan tandan kosong kelapa sawit sebagai bahan medium pertumbuhan telah dikaji. Kajian pengoptimuman telah dilakukan dengan menggunakan reka bentuk penuh faktorial dan pendekatan metodologi permukaan gerak balas. Jumlah maksimum ALA sebanyak 43.72 mg/kg telah dicapai dalam keadaan optimum seperti berikut: kandungan kelembapan 63.13 %, suhu inkubator 30.3 ℃, pH 7, ketumpatan inokulum 40 % (v/w), glisina 3.64 mM dan asid suksinik 23.03 mM selama 48 jam melalui SSF. Tiga model matematik iaitu Logistik, Gompertz dan Luedeking-Piret telah digunakan dan dibandingkan berdasarkan kepada kepadanan lengkung data eksperimen SSF yang terbaik. Model Logistik bergabung dengan model Luedeking-Piret telah dibentuk (R^2 >0.95) untuk menerangkan pertumbuhan mikrob *Rp*, penghasilan ALA dan penggunaan substrat untuk menghasilkan ALA oleh *Rp* melalui SSF dalam keadaan yang optimum. Parameter kinetik yang terlibat termasuklah kadar nilai maksimum tertentu (μ_m= 0.232 h^{-1}) dengan kepekatan biojisim maksimum *Rp* (X_{max}= 316.4 x 10^{-9} CFU.g^{-1}) untuk model pertumbuhan *Rp*; nilai pekali berkaitan dengan pertumbuhan (α= 8.249 mg.kg^{-1}.h^{-1}) dan nilai pekali yang tidak berkaitan dengan pertumbuhan (β = -1.660 mg.kg^{-1}.h^{-1}) untuk penghasilan ALA; pekali penggunaan substrat untuk pertumbuhan *Rp* dan pekali penggunaan substrak untuk penghasilan ALA ($Y_{X/S}$ = 0.132 and $Y_{P/S}$ = 0.141) bagi model penggunaan substrat juga dinilai. Nilai-nilai ini ditentusahkan di antara model yang diramalkan dengan data dari eksperimen menggunakan analisis kepadanan lengkung kuasa dua terkecil dan penyelesai persamaan kebezaan biasa (ODE45) dengan menggunakan perisian Matlab.

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LIST OF ABBREVIATIONS

Rp	-	*Rhodopseudomonas palustris*
ALA	-	5-Aminolevulinic Acid
BPSE	-	Bioprocess systems engineering
EFB	-	Empty Fruit Bunch
Mt	-	Million tonnes
SmF	-	Submerged Fermentation
LA	-	Levulinic acid
Gly	-	Glycine
Succ	-	Succinic Acid
RSM	-	Response Surface Methodology
HPLC	-	High-Performance Liquid Chromatography
MSW	-	Municipal Solid Waste
EM	-	Effective Microorganism
ATP	-	Adenosine triphosphate
ALAS	-	5-aminolevulinic acid Synthase
ALAD	-	5-aminolevulinic acid dehydratase
DMAB	-	dimethylaminobenzaldehyde
E.coli	-	*Escherichia coli*
PDB	-	Precursor-directed biosynthesis technique
ODE	-	Ordinary Differential Equation
PDE	-	Partial Differential Equation
GM	-	Glutamate medium
ANOVA	-	Analysis of Variance

LIST OF SYMBOLS

f(x)	-	Function of the independent variables
μ_m	-	Maximum specific growth rate (hr^{-1})
X	-	*Rp* biomass concentration (CFU/g)
t	-	Fermentation duration (hr)
X_{max}	-	Maximum concentration of *Rp* (CFU/g)
X	-	Concentration of biomass (CFU/g)
P	-	Concentration of ALA (mg/kg)
S	-	Concentration of feed substrates (mg/l)
α	-	Growth-associated coefficient
β	-	Non-growth associated coefficient
$Y_{X/S}$	-	Yield coefficient of biomass growth on substrates used
$Y_{P/S}$	-	Yield coefficient of product formed on substrates used
R_m	-	Specific product formation rate
P_{max}	-	Maximum concentration of product (ALA)
R^2	-	The determination of coefficient
h	-	hours
g/L	-	Gram per Litre
mg/kg	-	Milligram per kilogram
µM	-	Molar concentration

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CHAPTER I

INTRODUCTION

1.1 Research Background

In the 21st century, agricultural technology has rapidly developed in order to promote the agricultural activity and satisfy the worldwide food demand for growing population in both developing and developed countries. Even though traditional chemical fertiliser has been long applied to increase the crop yield and shorten the ripening time of the crop, it could still lead to serious environmental problems. Beneficial microbial inoculant has raised the attention of the researchers in order to produce high effective and efficiency of compost or fertiliser as an alternative to chemical fertilisers [1]. The application of beneficial microbial inoculants to produce biofertiliser or compost not only helps to stimulate the decomposition of organic waste and residues, detoxify the pathogen, suppress plant diseases, enhance the nutrient uptake of plant but also produce bioactive substrates to promote the plant growth, crop yield and maintain the sustainability of environmental [2].

Among the well-known beneficial microbial inoculants, *Rhodopseudomonas palustris* (*Rp*) is one of the predominant beneficial microorganisms that shows high potential to increase the plant uptake of nutrients, stimulate the plant growth and directly enhancing the crop growth and crop productivity [3,4]. Many studies have reported that the inoculation of *Rp* as biofertiliser or soil inoculants could promote the high yield of fruits and crops, enhance the acids tolerance in plant, able to fix the atmospheric nitrogen as their nitrogen source, directly reduce the use of chemical fertilizers and lead to more eco-friendly and sustainable agricultural practices [5]. Additionally, *Rp* is also well-known to produce potentially useful bioactive substrates like 5-aminolevulinic acid (ALA). ALA gained much attention as an effective, harmless, natural herbicide and insecticide under normal or stress condition, it has also been used to regulate, promoting the photosynthetic rate of plant growth for high crop yields [6-8].

For the purpose of these advantages given by microbial inoculants like *Rp*, a number of studies and research works have been carried out to study the effects of the application of microbial inoculants, plant growth and crops yield extensively [5]. In the market today, a variety of microbial biofertilisers are available that claim to stimulate plant growth and crop productivity. Many products are still lack of the scientific point of view due to several reasons:

(i) often the microbial inoculant involves mixed culture that is not specified in detail

(ii) the difficulties to reproduce their beneficial effect consistently

(iii) The complexity of the interactions effects among the microbial inoculants in the bio-system, thus, difficult to evaluate the product and its underlying behaviour or process in the compost [1,2].

Therefore, there is a need to carefully coordinate the standard methodology and devise a suitable technique to identify and better understanding the roles of each microbial and its interaction in the potential environmental, this will indirectly help in producing highly effective and efficient biofertiliser.

Bioprocess systems engineering (BPSE) has long been developed and recognised as a high promising methodology to better understanding the complexity of the biological process and the whole bio-system for over the past 20 years. BPSE offers a strategy to the living microorganism to enhance the cell growth, maximise the productivity of the target product and help in the production yield, while minimising the overall operation costs and reduce the environmental impact [9]. Additionally, BPSE has also implemented mathematical modelling as an essential tool to facilitate the fundamental understanding and provide insights into how the various behaviour within the complex bio-system from the engineering point of view [10]. Limited studies have investigated the production of ALA in the complex system like composting using the systematic methodology of BPSE. Hence, leveraging on the concept of BPSE one can better understand the underlying behaviour of ALA production by *Rp* in a complex system using series of the systematic methodology of BPSE.

1.2 Problem Statement

Malaysia has long been recognised as the world second top oil palm producer with 5.39 million hectares of oil palm planted area and a total of 423 palm oil mills operators [11]. Due to the large scale of oil palm production, the oil palm mills process have generated approximately 53 million tonnes (MT) of residues waste every year. Empty fruit bunch (EFB) is the main residues from the fresh fruit bunch after the palm oil extraction process and it is contributing an average of 23.8 MT among the generated solid residues waste from oil palm industries [11]. Improper discharged of the large amount of EFB to the environmental might create negative impact to the environment [11,12]. Composting has been proposed as one of the preferable and eco-friendly options to convert EFB into an inexpensive organic fertiliser for solid waste recycling, replacement of chemical fertiliser use, reducing EFB waste’s volume and helps to enhance the palm oil productivity in the plantation to achieve sustainable economic growth [13].

The promising characteristic of 5-aminolevulinic acid (ALA) to regulate and enhance the plant growth effectively has created the demand for ALA in agricultural practice [14]. Cultivation of photosynthetic bacteria like *Rhodopseudomonas palustris* (*Rp*) in submerged fermentation (SmF) are the widely studied fermentation process for ALA production but involved considerable high operation cost, there is a need to suggest a cheaper and economical approach to producing the desirable amount of ALA especially for the agricultural application. Solid state fermentation (SSF) is one of the microbial fermentation techniques which involve the microbial cultivation process on near absence of a free water solid medium. It involves low capital and operating cost expenses are the attractive reason to be chosen for ALA production [15].

The replacement of the solid medium by industrial residues like EFB not only provides a suggestion to handle EFB from oil palm industrial but also increases the economic value for EFB and making the ALA production process more cost effective. The primary concern of this research work is to better understand the roles of *Rp* and its respective interaction in the natural environment and indirectly help to produce highly effective and efficient compost. EFB can be considered as fibrous material that consists of less chemicals or mineral additives if compared to others oil palm residues like palm oil mill effluents [16]. The suggestion of ALA production by *Rp* on the EFB via SSF process could serve as one well-controlled system that mimics the composting process to further investigate the overall performance of *Rp* to produce ALA in compost.

There is a knowledge gap for the production of ALA by *Rp* in the solid state habitat with regard to the key factors promoting the ALA production. Inoculation of a beneficial microorganism to compost is expected to be beneficial by providing the suitable and optimum condition for the optimum metabolism of the microbes including the available water content of the environment, pH of the medium, temperature of the surrounding environment and available substrates uptake [1]. The environmental condition and supplementary substrate requirements for *Rp* in EFB to produce ALA have yet to be demonstrated.

The kinetic model commonly aims to describe the overall performance of a complex biological system, the interaction behaviour between the microbial and its respective metabolites quantitatively [17]. Kinetic models have been studied extensively in submerged fermentation (SmF) to produce ALA, relatively there is still a lack of kinetic studies to better understand the ALA production via SSF [8]. It is also a challenge to find the most appropriate model to give a better description of the observation in the experimental results. Therefore, it is more reasonable to compare different models to evaluate the well-fitted model to describe the overall performance of the particular process.

1.3 Objectives of the Study

This study aims to study the production of 5-aminolevulinic acid (ALA) by *Rhodopseudomonas palustris* (*Rp*) via solid state fermentation (SSF) using empty fruit bunch (EFB) as the solid support medium. The sub-objectives of this study include:

a) To optimise the physiochemical parameters and the concentration of supplementary substrate for the production of 5-aminolevulinic acid (ALA) by *Rhodopseudomonas palustris* (*Rp*) in solid state fermentation (SSF)

b) To develop the most plausible kinetic model to best describe the kinetic behaviours of *Rp* to produce the ALA in SSF process under the resulted optimised condition.

1.4 Scopes of the Study

The scopes of the study include:

a) To investigate the initial estimation of the parameter value ranges for the production of 5-aminolevulinic acid (ALA) in the solid state fermentation (SSF) using empty fruit bunch (EFB) as the solid support medium by *Rhodopseudomonas palustris* (*Rp*) using the classical one-factor-at-a-time method.

b) To determine the initial value range of the physiochemical parameters including the concentration of the impregnating nutrient medium (1-5 folds concentration), incubation temperature (25-45 ℃), inoculum density of *Rp* (20-60 %(v/w)), initial moisture content level (40-80%), initial pH (3-9), and the incubation period (1-5 days) to produce high yield of ALA by *Rp* in SSF using one-factor-at-a-time method.

c) To characterise the most significant physiochemical parameters among the selected parameters and further optimise the resulted significant physiochemical parameters (i.e.: moisture content, temperature, glycine, levulinic acid) to achieve a high yield of ALA using full-factorial method, Plackett-Burman design and Response Surface Methodology (RSM), Box-Behnken design.

d) To determine the optimum concentration of the supplementary substrates including glycine, succinic acid and levulinic acid to obtain a high yield of ALA via SSF under the resulted optimised fermentation condition.

e) To investigate the kinetic profiles of ALA synthesis, substrate uptake and *Rp* growth rate versus a time course under the optimised condition and characterise the total amount of ALA, substrates and *Rp* population quantitatively by using the colorimetric method, high-performance liquid chromatography (HPLC) and cell-plate counting method, respectively.

f) To select the most compatible kinetic model and estimate the kinetic parameters constant in the model to best describe the kinetic behaviour for the growth of *Rp*, substrate consumption and ALA formation for the production of ALA by *Rp* in SSF process.

g) To compare the experimental data from different studies to validate the robustness of the proposed model for the production of ALA by *Rp* in SSF.

1.5 Significant of the study

This research work contributes to improve the fundamental knowledge and understanding about the 5-aminolevulinic acid (ALA) production by *Rhodopseudomonas palustris* (*Rp*) via solid state fermentation (SSF) using empty fruit bunch (EFB) as solid support medium from the theoretical and practical perspectives. Comprehensive bioprocess, optimisation and modelling tools are highly recommended to make the process economically viable.

Firstly, there is a limited study to produce ALA by *Rp* via SSF using EFB as the solid support medium. Though there are studies considering the production of ALA via submerged fermentation (SmF), over the last few decades, there is an increasing trend to produce the value-added metabolites via SSF due to its advantages such as simpler process, less energy consumption, low capital cost using industrial agro-waste and less downstream processing. Based on the optimised result, the production of ALA by *Rp* in EFB can be applied for industrial large-scale production.

Secondly, the kinetic models are developed with important engineering characteristic to provide fundamental knowledge of the complex biological system. There is limited report conducted as a benchmark to further investigate the underlying kinetic performance for the production of ALA by *Rp* via SSF process using the engineering approaches. With increasing datasets of different metabolites production and more advanced mathematical description, the developed model could serve as a basic model to predict the performance of ALA production by *Rp* when there are changes in the rate and composition of the substrates.

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