UNIVERSITI PUTRA MALAYSIA

OPTIMIZATION OF BACTERIOCIN-LIKE INHIBITORY SUBSTANCE PRODUCTION BY Pediococcus acidilactici Kp10 FOR USE AS FOOD PRESERVATIVE

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By

SAHAR ABBASILIASI

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Doctor of Philosophy

May 2014

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DEDICATION

Dedicated to my father, my mother and my sister who have been a source of inspiration which contributed imensly to the success of this thesis

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Doctor of Philosophy

PRODUCTION OF BACTERIOCIN-LIKE INHIBITORY SUBSTANCE BY *Pediococcus acidilactici* Kp10 FOR USE AS FOOD PRESERVATIVE

By

SAHAR ABBASILIASI

May 2014

Chairman: Professor Arbakariya B. Ariff, Ph.D.
Faculty : Biotechnology and Biomolecular Sciences

The present study was carried out in view of the considerable interest in the search for safe, food-grade preservatives of biological origin. Towards this objective, lactic acid bacteria (LAB) were isolated from a number of milk by-products and fermented cocoa beans. The isolates were then screened for their ability in the production of bacteriocin-like inhibitory substance (BLIS). The physicochemical cell surface and adhesive properties of the bacterial strains were assessed using phenol, solvents, congo-red and n-hexadecane. The culture conditions for the production of BLIS by the isolated strain in the shake flask culture were optimized by the response surface methodology (RSM) and the artificial neural network (ANN). The influence of three independent variables (temperature, inoculum size and agitation speed) were examined in the optimization of culture conditions for the production of BLIS. The polymer–salt aqueous two phase system (ATPS) comprising of polyethylene–glycol (PEG) with sodium citrate was developed for direct recovery of BLIS. In this system, the influence of several parameters such as phase composition, tie-line length (TLL), volume ratio (V_R), crude sample loading, pH and the addition of sodium chloride (NaCl) on the partitioning behaviour of BLIS was also investigated. Finally, production of BLIS was conducted in stirred tank bioreactor for the identification of parameters in the scaling up. Data obtained were also analysed by mathematical models to study the kinetics of cell growth, lactose consumption and BLIS production.

A total of 222 LAB strains were isolated from fresh curd, dried curd, and ghara (a traditional flavor enhancer prepared from whey), and fermented cocoa beans. Eleven LAB isolates which have substantial antimicrobial properties were identified as *Lactococcus lactis*, *Lactobacillus plantarum*, and *Pediococcus acidilactici* by biochemical methods and 16S rRNA gene sequencing. Cell-free supernatant of *P. acidilactici* Kp10 exhibited the highest inhibition to *Listeria monocytogenes*, an important pathogen in the food industry. BLIS produced by *P. acidilactici* Kp10 was determined to be proteinaceous in nature and active over a wide range of pH. In this respect, *P. acidilactici* Kp10 was selected for the development of a fementation process for BLIS production. *P. acidilactici* Kp10 was found to be catalase-negative, able to produce β-galactosidase, resistant to bile salts (0.3%) and acidic conditions (pH 3), and susceptible to most antibiotics. *P. acidilactici* Kp10 also displayed good tolerance to the gastrointestinal environment, adhesion ability to intestinal mucosa

and capable to inhibit pathogens.

The ANN-predicted levels of agitation speed, inoculum size, and temperature for optimal BLIS production by *P. acidilactici* Kp10 in shake flask fermentation were 120 rpm, 3% and 28.5 ^{o}C respectively. On the other hand, the predicted levels for the same variables using RSM were 126 rpm, 5.5% and 28.5 ^{o}C respectively. The predicted BLIS activity (5,262.64 AU/mL) obtained by the ANN was comparable with that obtained by the RSM (6,311.5 AU/ mL). However, The observed BLIS activity at the predicted optimum levels of the tested variables by RSM and ANN was 5,118.5 AU/ mL. ANN was considered to be a preferred optimization tool than RSM as the activity predicted by ANN was closer to the observed values at all experimental levels of three variables. The overall production of BLIS in optimized fermentation was enhanced at least by 30 times in comparison to those obtained in non-optimized fermentation.

Under optimum conditions of the ATPS, purification of BLIS was achieved at 26.5% PEG (8,000)/ 11% citrate system comprising of TLL at 46.38% (w/w), V_R of 1.8, without the addition of NaCl and 1.8% crude load at pH 7.0. BLIS from *P. acidilactici* Kp10 was partially purified by the ATPS up to 8.43-fold with a yield of 81.18%. BLIS production by *P. acidilacti* Kp10 in stirred tank bioreactor was a growth associated process where the production was greatly influenced by the aeration and agitation conditions of the bioreactor and the level of dissolved oxygen in the culture.

Results from this study demonstrated that *P. acidilactici* Kp10 could be used as the potential probiotic for applications in food industry. Efficient large scale production of BLIS by *P. acidilactici* Kp10 could be performed using stirred tank bioreactor with controlled cultivation at optimal conditions. BLIS from *P. acidilactici* Kp10 could be efficiently extracted and purified for commercial application using ATPS, which is a more economical method.

Abstrak Tesis Untuk di Kemukakan Kepada Senat Universiti Putra Malaysia
Sebagai Memenuhi Keperluan Anugerah Ijazah Doktor Falsafah

PRODUKSI BAHAN PERENCAT SERUPA-BAKTERIOSIN OLEH *PEDIOKOKUS ASIDILAKTISI* KP10 YANG DIISOLASI DARIPADA SUMBER MAKANAN

Oleh

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Kajian ini dijalankan dengan mengambil kira kepentingannya untuk mencari pengawet bergred-makanan berasaskan sumber biologi yang selamat. Untuk tujuan ini, bakteria asid laktik (BAL) telah diisolasi daripada beberapa produk sampingan susu dan biji koko yang telah difermentasi. Seterusnya isolat yang diperolehi telah disaring untuk mengenalpasti strain bakteria yang menghasilkan bahan perencat serupa bakteriosin (BLIS). Ciri fisikokimia permukaan sel dan ciri berperekat strain bakteria tersebut masing-masing telah dikaji menggunakan pelarut fenol, kongo-merah, n-heksadikana dan juga dengan mengunakan dua jenis sel epitelium mamalia. Keadaan kultur untuk penghasilan BLIS oleh strain bakteria tersebut dalam kelalang goncang telah dioptimumkan dengan menggunakan metodologi respons permukaan (MRP) dan jaringan neural tiruan (JNT). Kesan tiga pemboleh-ubah bebas (suhu, saiz inokulum dan kelajuan agitasi) telah dikaji dalam pengoptimuman keadaan kultur untuk penghasilan BLIS. Sistem pernulenan dwi-fasa garam-polimer (SDFA) yang terdiri daripada polietelina-glikol (PEG) dengan sodium sitrat telah dibentuk untuk perolehan terus BLIS. Dalam sistem ini pengaruh beberapa parameter seperti komposisi fasa, *tie-line length* (TLL), nisbah isipadu (I*n*), muatan sampel kasar, pH dan penambahan sodium klorida ke atas perilaku pemisahan BLIS juga telah dikaji. Akhir sekali kajian produksi BLIS berskala besar telah dijalankan dalam bioreaktor berpengaduk. Data yang diperolehi telah dianalisis menggunakan model matematik untuk mengkaji pembiakan sel, penggunaan laktosa dan produksi BLIS.

Sejumlah 222 strain BAL telah diisolasi daripada produk sampingan susu terdiri daripada dadih segar, dadih kering dan *ghara* (penambah perisa tradisi diperbuat daripada air dadih) dan koko yang difermentasi. Sebelas (11) BAL yang mempamerkan ciri antimikrob telah dikenalpasti sebagai strain *Laktokokus laktis, Laktobasilus planatarum* dan *Pediokokus asidilaktisi* menggunakan kaedah biokimia dan jujukan gen 16S dan rRNA. Supernatan *P. asidilaktisi* Kp10 bebas-sel mempamerkan perencatan paling tinggi ke atas *Listeria monocytogenes* yang merupakan patogen terpenting dalam industri makanan. BLIS yang dirembes oleh *P. asilaktisi* Kp10 adalah dalam bentuk protein dan aktif pada julat pH yang luas. Dengan ini *P. asidilaktisi* telah dipilih untuk membangunkan proses fermentasi untuk penghasilan BLIS. *P. asdilaktisi* didapati katales-negatif, berupaya menghasilkan B-galaktosides, berdaya tahan terhadap garam hempedu (0.3%) dan keadaan berasid

(pH 3) dan boleh alah kepada kebanyakan antibiotik. *P. acidilaktisi* Kp10 juga menunjukkan toleransi yang menggalakkan kepada persekitaran gastrousus di samping berkebolehan melekat pada mukosa usus dan merencat beberapa jenis patogen. Ciri bermanfaat yang dipamerkan oleh *P. asidilaktisi* Kp10 melayakkan strain bakteria ini untuk dicalonkan sebagai probiotik.

Aras jangkaan-JNT, kelajuan agitasi, saiz inokulum dan suhu untuk mengoptimumkan produksi BLIS oleh *P. asidilaktasi* Kp10 bagi fermentasi dalam balang goncang adalah masing masing 120 kitaran/min., 3% dan 28.5 ^{o}C. Aras jangkaan bagi parameter boleh ubah yang sama menggunakan MRP adalah masing masing 126 kitaran/min, 5.5% dan 28.5 ^{o}C. Jangkaan aktiviti BLIS (5262.4AU/mL) yang diperolehi menggunakan JNT adalah bersamaan dengan yang diperolehi menggunakan MRP (6311.55 AU/mL). Namun demikian cerapan aktiviti BPBB pada aras optimum jangkaan bagi pemboleh ubah yang diuji oleh JNT dan MRP adalah 5118.5 AU/ml. Dengan ini JNT disifatkan sebagai alat pengoptimuman yang lebih baik berbanding dengan MRP; ini mengambil kira aktiviti jangkaan JNT adalah lebih rapat kepada nilai cerapan pada kesemua aras eksperimental untuk ketiga tiga pemboleh ubah. Pada keseluruhannya produksi BLIS dengan fermentasi yang dioptimumkan telah meningkatkan sekurang kurangnya 30 kali ganda berbanding dengan fermentasi yang tidak dioptimumkan.

Dibawah kondisi optimum SDFA, punulenan BLIS diperolehi pada 26.5% PEG (8,000)/11% sistem sitrat merangkumi TLL pada 46.38% (w/w), I*n* 1.8 tanpa penambahan sodium klorida dan 1.8% muatan kasar pada pH 7.0. Produksi BLIS separa tulen yang diperolehi daripada *P. asidilaktisi* Kp10 melalui SDFA adalah 8.43 kali ganda dengan jumlah hasil 81.18%. Produksi BLIS dalam tangki aduk bioreaktor adalah proses berkait pembiakan mengambil kira produksi PBPP sangat dipengaruhi oleh kondisi pengudaraan dan agitasi dalam dan aras oksigen terlarut dalam kultur. Kesimpulannya SDFA adalah mudah dari segi operasi, menjimatkan kos, masa dan kurang merbahaya kepada persekitaran.

Hasil daripada kajian ini menunjukkan *P. asidilaktisi* Kp10 berkemungkinan besar boleh digunakan sebagai probiotik untuk aplikasi dalam industri makanan. Produksi BPBB berskala besar yang berkesan boleh dilakukan menggunakan tangki adu bioreaktor dengan kultur terkawal pada kondisi yang optimum. BLIS daripada *P. asidilaktisi* Kp10 boleh diekstrak dengan berkesan dan ditulenkan untuk aplikasi komersil menggunakan SDFA yang merupakan kaedah yang lebih ekonomikal.

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I certify that a Thesis Examination Committee has met on 28 May 2014 to conduct the final examination of Sahar Abbasiliasi on her thesis entitled "Optimization of Bacteriocin-Like Inhibitory Substance Production by *Pediococcus acidilactici* Kp10 for Use as Food Preservative" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the Doctor of Philosophy.

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AU	Arbitrary unit/ Activity unit
ANN	Artificial neural network
AAD	Absolute average deviation
ATPS	Aqueous two phase system
AC	Auto-aggregation coefficient
AMPTS	Aqueous micellar two-phase systems
ANOVA	Analysis of variance
AA	Acetic acid
ATCC	American type culture collection
AU/mL	Activity units per mL
α	Growth associated BLIS production constant
BSA	Bovine serum albumin
BW	Box-Wilson
BLIS	Bacteriocin-like inhibitory substance
BATS	Bacterial cell adhesion to solvent
BATH	Bacterial adhesion to hydrocarbons
BSH	Bile salt hydrolytic
BP	Back propagation
BW	Box-wilson
BHB	Brain heart broth
BHI	Brain Heart Infusion
β	Non-growth associated BLIS production constant
CA	Citric acid
CAGR	Compound annual growth rate
CFCS	Cell free culture supernatant
CGD	Conjugate gradient descent
CCD	Central composite design
CDA	Critical dilution assays
CD	Critical dose
CFU/mL	Colony-forming unit per milliliter
CH_3CHO	Acetaldehyde
CO_2	Carbon dioxide
$CH_3–CH(OH)–COOH$	Lactic acid
$CH_3–COOH$	Acetic acid
$CH_3–CH_2–COOH$	Propionic acid
$C_6H_8O_7$	Citric acid
CH_3COONa	Sodium acetate
d	Dose
DCW	Dry cell weight
DO	Dissolved oxygen
DOT	Dissolved oxygen tension
DFM	Direct-fed microbial
DMEM	Dulbecco's modified eagle medium
ELISA	Enzyme-linked immunosorbent assay
E.	*Enterococcus*

FPLC	Fast performance liquid chromatography
FDA	Food and drug administration
FAO	Food and agriculture organization
g	Gram
GRAS	Generally recognized as safe
GA	Genetic algorithm
g	Relative centrifugation force
g/mol	Gram per mol
HPLC	High performance liquid chromatography
HSD	Honestly significant difference
h	Hour
HSD	Honestly significant difference
H_2O_2	Hydrogen peroxide
HT-29	Human colon adenocarcinoma cell line
I	Intermediate
IU	International units
IPTG	Isopropyl β-D-1-thiogalactopyranoside
KH_2PO_4	Potassium dihydrogen phosphate
K_2HPO_4	Potassium hydrogen phosphate
K	Partition coefficient
kDa	Kilo dalton
L	Litre
Lb.	*Lactobacillus*
Lc.	*Lactococcus*
Leuc.	*Leuconostoc*
m	Growth associated lactose consumption coefficient
M	Minute
μ_{max}	Highest specific growth rate
$MgSO_4.7H_2O$	Magnesium sulfate
MRS	De man, rogosa and sharpe
MPN	Multilayer perception network
MSE	Mean square error
mm	Millimeter
min	Minute
mg	Milligram
µg	Microgram
µL	Microlitre
µm	Micrometer
mM	Millimolar
MW	Molecular weights
ND	Not detected
$NaH_2C_6H5O_7$	Sodium citrate
$(NH_4)_2SO_4$	Ammonium sulphate
$NO_3C_6H_5O_7.2H_2O$	Sodium citrate
n	Non-growth associated of lactose consumption coefficient
NaCl	Sodium chloride
^oC	Degree centrigrade
ORFs	Open reading frames
OD	Optical density

PEG	Polyethylene glycol
P.	*Pediococcus*
PBS	Phosphate-buffered saline
PBD	Plackett-Burman design
PSA	Path of steepest ascent
PAB	Propionic acid bacteria
PCR	Polymerase chain reaction
P	Product
%	Percentage
P_m	Maximum product formed
pI	Power of ions
P_{FT}	Purification factor
q_O	Specific oxygen consumption rate
q_P	Specific product formation rate
q_S	Specific substrate consumption rate
R	Response
R^2	Correlation determination
R	Resistant
RMSE	Root mean square error
RPMI	Roswell park memorial institute medium
RSM	Response surface methodology
S	Sensitive
SA	Specific activity
S	Selectivity
SEP	Standard error of prediction
SEM	Scanning electron microscope
S	Substrate
SDS-PAGE	Sodium dodecyl sulfate-polyacrylamide gel electrophoresis
S_m	Maximum substrate consumed
S_o	Initial substrate concentration
SSE	Sum of squares error
STR	Stirrer tank reactor
S.E	Standard error
TSBYE	Trypticase soy broth yeast extract
TS	Total sugars
TN	Total nitrogen
TLL	Tie-line length
TEM	Transmission electron microscope
TEMED	tetramethylethylenediamine
Tween 80	Polyoxyethylene sorbitan mono-oleate
V_o	Initial volume
V	Volume
V_B	Ratio of volume in the bottom phase
V_R	Volume ratio
v/v	Volume per volume
Vero cells	African green monkey kidney cell line
V_T	Ratio of volume in the top phase
w/v	Weight per volume

WHO	World health organization
X	Cell concentration
X_m	Maximum cell concentration
X_o	Initial cell concentration
X-gal	5-bromo-4-chloro-3-indolyl β-D-galactopyranoside
Y	Yield
$Y_{P/X}$	Cell productivity
$Y_{X/S}$	Cell yield

CHAPTER 1

INTRODUCTION

Of late there has been increasing concern on the part of government agencies and food manufacturers on food safety. Coupled with continuous consumer demand for natural and safe food preferably with minimal processing led to the application of natural antimicrobial polypeptides in the inhibition of the growth of undesirable microorganisms (Pongtharangkul and Demirci, 2006; Powell, 2006). Reduced application of food preservation techniques and substances is no easy task apart from many potential dangers it may pose. An estimated 5 to 10 % of food production worldwide is lost to spoilage by fungi (Schnürer and Magnusson, 2005). Food pathogens such as *Listeria* spp., resistant to refrigeration temperatures and high salt concentrations are responsible for 2,500 illnesses of which 500 have been recorded as fatal in the United States alone (Deegan *et al.*, 2006). Thus the need for natural preservatives such as bacteriocins is high. However, bacteriocins should not be seen as the main control measure for food preservation but rather as an extra obstacle for the multiplication of spoilage or pathogenic bacteria (Coetzee, 2007; Deegan *et al.*, 2006). To inactivate foodborne pathogens, novel technologies such as biopreservation systems, non-thermal technologies or their combined treatments have been studied. Examples of biopreservation include the use of lactic acid bacteria (LAB) or their antagonistic metabolites which are principally lactic acid, hydrogen peroxide (H_2O_2) and bacteriocins (Chung, 2003).

Bacteriocins which are antimicrobial proteins or protein complexes produced by several gram-positive and gram-negative bacteria are known to possess specific characteristics which contribute to their food preservative properties. In food processing many bacteriocins are resistant to high temperature and remain functional over broad pH ranges. Like other proteins in the diet, many enzymes could digest the bacteriocins and hence not detrimental to beneficial gut microflora. Bacteriocins are non-toxic and present in many foods and have been unwittingly consumed by mankind for thousands of years being odorless, colorless, and tasteless (Cleveland *et al.*, 2001). Being natural products bacteriocins are more accepted by consumers compared to chemical preservatives. Bacteriocins play a critical role in mediating microbial interactions and maintanance of microbial diversity at the population and community levels (Kerr et al, 2002). Bacteriocins may serve as anticompetitors enabling the invasion of a strain or a species into an established microbial population or community. They may also play a defensive role and act to prohibit the invasion of other strains or species into an occupied niche or limit the advance of neighboring cells (Riley, 2011). This diverse group of protein toxins could have a potential application in human health, veterinary medicine, crop management, agriculture practices, poultry production, food preservation and bioremediation (Riley and Wertz, 2002). It appeared that much of the renewed interest in bacteriocins is a direct response to their perceived potential applications either to food preservation of or to the prevention and treatment of bacterial infections.

Although bacteriocins are produced by many gram-positive and gram-negative bacterial species, only those produced by LAB are of particular importance in the food industry (Abbasiliasi *et al.*, 2010). In fact LAB bacteriocins enjoy a food-grade

which offer food scientists the choice of allowing the development of desirable flora in fermented foods or preventing the development of spoilage and pathogenic bacteria in foods (Settanni and Corsetti, 2008). Adding food grade bacteriocins to food products could enhance the nutritional properties of products which decrease the use of chemical preservatices and intensity of treatment by heat (Ross *et al*., 1999). In many instances, these bacteriocins could complement other food preservative methods (e.g., high pressure processing and pulsed electric fields) to reduce the prominance of spoilage or pathogenic bacteria (Bennik *et al*., 1999). The combined effect of bacteriocin and preservation methods are more detrimental to the microorganisms leading to their death (Gálvez *et al*., 2007). Bacteriocins are also known to improve the hygienic quality of food and extend their shelf-life (Hanlin *et al*., 1993; Song and Richard, 1997; Vignolo *et al*., 2000; Zhang, 2008).

Bacteriocins from LAB have widespread potential for applications in food preservation and improvement of safety and quality. Indeed, bacteriocins may be viewed as an innate immunity system which can be inbuilt into food system to self-protect them against contamination and outgrowth with undesirable flora (Vescovo *et al*., 1996). Bacteriocins are also an attractive focus for drug development as they are active against most pathogens, already exist in nature, are remarkably stable. non toxic to human cells with the potential to go for industrial production. The beneficial effects of these peptides are their small size with their actions directed towards the cell membrane, being easily digested in human intestine and it does not induce any toxic effect or allergy (Abbasiliasi *et al*., 2010; Chen and Hoover, 2003).

To date the only approved LAB bacteriocin as food additives are nisin and pediocin (Guerra and Pastrana, 2002a). Nisin is the most widely used bacteriocin and has been accorded the generally recognized as safe (GRAS) status. However, nisin has several disadvantages being unstable at neutral to alkaline pHs, its antimicrobial activity decreased when added into complex foods, its solubility decreased whithin a wide pH range and it is active only against only gram-positive bacteria. On the other hand pediocins have generally been accepted as food biopreservative as it has been extensively studied and characterized. Pediocin produced by *Pediococcus* sp. are broad spectrum antimicrobial peptides *Listeria monocytogenes* (*L. monocytogenes*), *Clostridium perfringens*, *Enterococcus faecalis* (*E. faecalis*) and *Staphylococcus aureus* which are food-spoilage and pathogenic bacteria. Pediocins are also stable within a wide range of temperature and pHs (Guerra and Pastrana, 2002a). For economical application in foods pediocin have to be produced in large amounts.

In the food industry, *L. monocytogenes* is a causative agent of listeriosis as it is present in contaminated dairy milk and meat products which is responsible for the outbreak of foodborne illness. Members of the genus *Listeria* show a varying degree of sensitivity to natural antimicrobials produced by LAB including the broad-spectrum pediocin of *Pediococcus acidilactici* (*P. acidilactici*) which is used in the production of fermented sausages (Somkuti and Steinberg, 2003).

With the realization on the economic importance of the much soughtafter bacteriocin in the food industry, the general objective of this study was directed towards the identification of bacteriocins producing LAB from a locally dried curd, fresh curd, ghara and cocoa beans, it is hypothesized that large scale bacteriocin-like inhibitory

substance (BLIS) production could be developed by submerged fermentation in stirred tank bioreactor.

Based on the above hypothesis the specific objectives of the study in this thesis were to:

1) isolate, identify and charaterize BLIS producing LAB from various food sources for possible application in the food industry.

2) examine the adhesion properties of the selected isolate as a potential probiotics.

3) optimize the culture conditions for production of BLIS by the selected isolate using the shake flask fermentations.

4) investigate the possibility of using aqueous two phase system (ATPS) comprising of polyethylene glycol (PEG) and sodium citrate ($NaH_2C_6H5O_7$) for the recovery and purification of BLIS from the fermentation broth.

5) evaluate the effect of agitation and aeration on BLIS production by the selected isolate in a 2 L stirred tank bioreactor.

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