



UNIVERSITI PUTRA MALAYSIA

***MOLECULAR CHARACTERIZATION OF BACTERIOCIN LOCI IN
LACTOBACILLUS PLANTARUM I-UL4***

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**MOLECULAR CHARACTERIZATION OF BACTERIOCIN LOCI IN
LACTOBACILLUS PLANTARUM I-UL4**

By

TAI HUI FONG

**Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, In
Fulfilment of the Requirements for the Degree of Master of Science**

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Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfillment of the requirement for degree of Master of Science

MOLECULAR CHARACTERIZATION OF BACTERIOCIN LOCI IN *LACTOBACILLUS PLANTARUM* I-UL4

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June 2013

Chairman: Assoc. Prof. Foo Hooi Ling, PhD
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Bacteriocin is a group of proteinaceous antimicrobial peptides produced inhibiting the growth of closely related bacterial strains. Bacteriocin and bacteriocinogenic Lactic Acid Bacteria (LAB) have received special attention due to their potential applications as biopreservative, therapeutic agent and antibiotic-replacer in livestock animals. *Lactobacillus plantarum*, a member of LAB is found in various ecological niches with more than 10 types of bacteriocins have been reported for this species. *L. plantarum* I-UL4 isolated from the fermented tapioca exhibits a wide spectrum of bacteriocin activity against Gram-positive and Gram-negative bacteria as well as food-borne pathogens. It was reported to carry two bacteriocin structural genes, *plW* and *plnEF* encode for plantaricin W and plantaricin EF, respectively. However, the information regarding the bacteriocin biosynthetic genes for plantaricin W and plantaricin EF such as immunity, secretion and regulatory genes as well as the organisation of the respective bacteriocin loci are not available.

Hence, the bacteriocin loci of *L. plantarum* I-UL4 containing *plW* and *plnEF* structural genes were analysed in this study. The presence of 24 selected plantaricin (*pln*) biosynthetic genes (structural, immunity, secretion and regulatory genes) described for *plnS*, *pln423*, *plW* and *plnEF* loci were amplified and sequenced. The result revealed the presence of eight *pln* genes and two *pln* genes from *plnEF* and *plW* locus, respectively. On the contrary, the *pln* genes of *plnS* locus, *pln423* locus and nine *pln* genes of *plnEF* locus were absent from the studied strain as confirmed by gradient PCR.

The DNA sequence of the flanking region of these *pln* genes were amplified and sequenced. The results revealed two contigs of 2.7 kilobase (kb) (UL4-*plW* locus) and 17.5 kb (UL4-*plnEF* locus), respectively. The UL4-*plW* locus contains three open reading frames (ORFs) arranged in the same orientation which showed remarkable DNA ($\geq 99.7\%$) and amino acid ($\geq 99.3\%$) sequence identities to the *plW* locus of *L. plantarum* LMG2379. On the contrary, 21 ORFs were predicted on the UL4-*plnEF* locus. Each ORF has remarkable DNA and amino acid sequence identities to the reported ORFs of *plnEF* loci in *L. plantarum* C11, WCFS1, V90, J51, NC8, J23 and

JDM1 (reported *plnEF* loci). Five operons were deduced in the ULA-*plnEF* locus: *orf345*, *plnLR*, *plnULAIF-ULAHK-plnD*, *plnEFI* and *plnGHSUVW*. The ULA-*plnEF* locus was demonstrated to contain different number of bacteriocin gene exhibiting different organisations from the reported *plnEF* loci. Specifically, *plnF* (bacteriocin structural gene encoding plantaricin EF) of the ULA-*plnEF* locus showed mutation which contributed to a longer plnF peptide with isoelectric point was 0.28 lower than the plnF of the reported *plnEF* loci. Interestingly, the ULA-*plnEF* locus was shown to be a hybrid of the *plnEF* locus of *L. plantarum* JDM1 and J51, where the left-half and right-half of ULA-*plnEF* locus resembled the *plnEF* locus of *L. plantarum* JDM1 and J51, respectively. Southern hybridisation with specific DNA probe showed that both ULA-*plW* and ULA-*plnEF* loci were chromosomally encoded. The ULA-*plW* locus encoded lantibiotic plantaricin W, while the ULA-*plnEF* locus encoded class IIb plantaricin EF and a putative two-peptide plantaricin *orf34*.

In conclusion, the concurrent presence of the ULA-*plW* and the mosaic ULA-*plnEF* loci suggested that the *L. plantarum* I-ULA was a novel multi-bacteriocinogenic LAB.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Master Sains

**PENCIRIAN MOLEKULAR LOKUS PRODUKSI BAKTERIOSIN DARIPADA
LACTOBACILLUS PLANTARUM I-UL4**

Oleh

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Jun 2013

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Bakteriosin adalah sekumpulan peptida antimikrob yang dihasilkan untuk merencat pertumbuhan strain bakteria yang berkait rapat. Bakteriosin dan bakteria asid laktik (LAB) yang berbakteriosin telah menerima perhatian khas kerana aplikasi potensi mereka sebagai ejen biopreservative, terapeutik dan pengganti antibiotik pada haiwan ternakan. *Lactobacillus plantarum*, ahli LAB boleh didapati dalam pelbagai lapisan ekologi dengan lebih daripada 10 jenis bakteriosin telah dilaporkan untuk spesis ini. *L. plantarum* I-UL4 yang dipencilkan daripada ubi kayu tertapai menunjukkan spektrum aktiviti bakteriosin yang luas terhadap bakteria Gram-positif dan Gram-negatif serta patogen makanan. Ia telah dilaporkan mempunyai dua gen struktur bakteriosin, *plW* dan *plnEF* yang masing-masing mengekodkan plantaricin W dan plantaricin EF. Walau bagaimanapun, maklumat mengenai gen biosintesis bakteriosin untuk plantaricin W dan plantaricin EF seperti imuniti, rembesan dan gen kawalan serta organisasi lokus bakteriosin masih tidak diketahui.

Oleh itu, lokus bakteriosin *L. plantarum* I-UL4 yang mengandungi gen struktur *plW* dan *plnEF* dianalisis dalam kajian ini. Kehadiran 24 gen biosintesis plantaricin (*pln*) (gen struktur, imuniti, rembesan dan kawalan) yang diumumkan bagi lokus-lokus *plnS*, *pln423*, *plW* dan *plnEF* diamplifikasikan dan jujukannya ditentukan. Keputusan menunjukkan kehadiran lapan dan dua gen *pln* masing-masing daripada lokus *plnEF* dan lokus *plW*. Sebaliknya, gen-gen *pln* daripada locus *plnS*, locus *pln423* dan sembilan gen-gen *pln* daripada locus *plnEF* didapati tidak hadir pada strain yang dikaji seperti yang disahkan oleh kecerunan PCR.

Jujukan DNA untuk DNA yang mengelilingi gen-gen *pln* ini diunjukkan. Keputusannya menunjukkan dua contig yang masing-masingnya mempunyai sebanyak 2.7 kilo pasangan bes (kb) (locus UL4-*plW*) dan 17.5 kb (locus UL4-*plnEF*). Locus UL4-*plW* mengandungi tiga bingkai bacaan terbuka (ORF) yang disusunkan dalam orientasi yang sama di mana ia menunjukkan identiti jujukan DNA ($\geq 99.7\%$) dan urutan asid amino ($\geq 99.3\%$) yang tinggi dengan lokus *plW* *L. plantarum* LMG2379. Manakala, 21 ORF telah diramalkan pada lokus UL4-*plnEF*. Setiap ORF mempunyai identiti jujukan DNA

dan urutan asam amino yang tinggi dengan ORF yang dilaporkan untuk lokus *plnEF* *L. plantarum* C11, WCFS1, V90, J51, NC8, J23 dan JDM1 (lokus-lokus *plnEF* yang diumumkan). Lima operon telah disimpulkan dari lokus UL4-*plnEF*: *orf345*, *plnLR*, *plnULAIF-UL4HK-plnD*, *plnEFI* dan *plnGHSUVW*. Lokus UL4-*plnEF* telah dibuktikan mengandung jumlah gen bakteriosin yang berbeza dan mempamerkan organisasi yang berbeza daripada lokus-lokus *plnEF* yang dilaporkan. Khususnya, *plnF* (bakteriosin struktur gen yang mengkodkan plantaricin EF) daripada lokus UL4-*plnEF* menunjukkan mutasi yang menyumbang kepada peptida *plnF* yang lebih panjang dengan titik isoelektriknya adalah 0.28 lebih rendah daripada *plnF* yang dilaporkan. Yang menariknya, lokus UL4-*plnEF* menyerupai cantuman lokus *plnEF* daripada *L. plantarum* JDM1 dan J51, di mana separuh kiri dan kanannya daripada UL4-*plnEF* locus masing-masing menyerupai separuh kiri dan separuh kanan lokus *plnEF* *L. plantarum* JDM1 dan J51. Hibridisasi Selatan dengan menggunakan probe DNA tertentu menunjukkan bahawa kedua-dua lokus UL4-*plW* dan lokus UL4-*plnEF* adalah dikodkan pada kromosom. Lokus UL4-*plW* mengkodkan lantibiotic plantaricin W, manakala lokus UL4-*plnEF* mengkodkan plantaricin EF yang berkelas IIB dan plantaricin putatif *orf34* yang berpeptida dua.

Kesimpulannya, kehadiran serentak lokus UL4-*plW* dan lokus UL4-*plnEF* mencadangkan bahawa *L. plantarum* I-UL4 adalah satu LAB beraneka bakteriosin yang novel.

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I certify that a Thesis Examination Committee has met on 27 June 2013 to conduct the final examination of Tai Hui Fong on her thesis entitled “Molecular Characterization of Bacteriocin Loci in *Lactobacillus plantarum* I-UL4” 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 Master of Science.

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LIST OF ABBREVIATIONS

°C	Degree Celsius
<i>G</i>	G-force
μL	Microlitre
μM	Micromolar
%	Percentage
≥	More than or equal to
<	Less than
>	More than
[name of the strain]-[ORF or peptide]	The ORF of peptide of a strain
ATP	Adenosine triphosphate
AviCys	2-aminovinyl- <i>D</i> -cysteine
AviMeCys	<i>S</i> -aminovinyl-methyl- <i>D</i> -cysteine
Bp	Basepair
Cm	Centimeter
Da	Dalton
dH ₂ O	Distilled water
Dha	dehydroalanine
Dhb	dehydrobutyrine
DNA	Deoxyribonucleic acid
dNTP	Deoxyribonucleotide triphosphate
EDTA	Ethylenediaminetetraacetic acid
G	Gram
HPK	Histidine protein kinase
HCl	Hydrochloric acid
Hr	Hour
IF	Induction factor
kDa	Kilodalton
LAB	Lactic acid bacteria
Lan	Lanthionine
M	Molar
MeLan	α-methylanthionine
Mg	Milligram
MgCl ₂	Magnesium chloride
Min	Minute
mL	Mililitre
Mm	Milimetre
mM	Milimolar
MRS	De Man, Rogasa and Sharpe medium

MRSA	Methicillin resistant <i>Staphylococcus aureus</i>
MW	Molecular mass
N	Normality
NaCl	Sodium chloride
Na ₂ HPO ₄	Disodium hydrogen phosphate
NaH ₂ PO ₄	Sodium dihydrogen phosphate
NaOAc	Sodium acetate
NaOH	Sodium hydroxide
NCBI	National Center for Biotechnology Information
ng	Nanogram
OD	Optical density
ORF	Open reading frame
PCR	Polymerase chain reaction
pI	Isoelectric point
<i>pln</i>	plantaricin
RBS	Ribosome binding site
reported <i>plnEF</i> loci	<i>plnEF</i> locus of <i>L. plantarum</i> JDM1, C11, WCFS1, V90, J51, NC8 and J23
rDNA	Ribosomal deoxyribonucleic acid
rRNA	Ribosomal ribonucleic acid
RNase	Ribonuclease
RR	Response regulator
RT	Room temperature
SDS	Sodium dodecyl sulphate
SSC	Saline-sodium citrate
TAE	Tris-Acetate-EDTA
TCR	Three component regulatory system
TE	Tris-EDTA
TS+3147	Teat seal formulated with lacticin 3147
U	Unclassified
UV	Ultraviolet
V	Volt
v/v	Volume per volume
w/v	Weight per volume
x	Times
<i>Bacillus</i>	<i>B.</i>
<i>Carnobacterium</i>	<i>C.</i>
<i>Escherichia</i>	<i>E.</i>
<i>Enterococcus</i>	<i>Ent.</i>
<i>Lactobacillus</i>	<i>L.</i>
<i>Lactococcus</i>	<i>Lc.</i>

Leuconostoc
Listeria
Pediococcus
Pseudomonas
Staphylococcus
Streptococcus
Salmonella

Leu.
Ls.
P.
Ps.
Stap.
Strep.
S.



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CHAPTER 1

INTRODUCTION

During the past decade, many studies have focused on natural antimicrobial substances secreted by food-grade bacteria to inhibit undesirable microorganisms due to the general-consumer-demand of decreasing the use of chemical additives in food preservation. The antimicrobial effect of Lactic Acid Bacteria (LAB) is greatly appreciated by human being since 10,000 years ago and has been exploited to extend the shelf life of many foods through fermentation processes. It has been known for a long time that LAB are capable of producing antimicrobial compounds and among these, the ribosomally synthesised antimicrobial peptides generally termed as bacteriocins received special attention from both the scientific and food industries (Riley and Wertz, 2002). Both bacteriocins and bacteriocinogenic LAB can be used as natural biopreservatives in food industry, therapeutic agents and antibiotic-replacer in livestock animals (Lohans and Vederas, 2012; Joerger, 2003)

There are numerous factors that drive the researchers to carry out research on bacteriocin. Their relatively narrow and highly specific killing spectrum compared to antibiotic had raised the interest of using bacteriocin as antibiotic replacer in human and animal health. Several studies revealed the potential application of bacteriocin to replace the use of antibiotics in the prevention and/or treatment of various infectious disease such as peptic ulcer, mastitis infections (Fernandez *et al.*, 2008; Mojgani *et al.*, 2006), skin inflammation and acne (Oh *et al.*, 2006) and dental caries (Bastos *et al.*, 2009).

The works on bacteriocins are mainly focused on the genetic modifications of bacteriocins as to gain detailed insight of the amino acid residues that are responsible for their biological activities and mode of actions. The knowledge gained by studying genetically modified bacteriocin was used to improve engineered bacteriocin and designed drugs (Field *et al.*, 2010; Papagianni and Anastasiadou, 2009; Gillor *et al.*, 2005). In addition, there are interests in heterologous expression of bacteriocin in industrially important bacterial and yeast starter cultures (Rodriguez *et al.*, 2003). However, it should be noted that in order to design a new and improved bacteriocin as well as bacteriocin expression system, a deeper understanding of the bacteriocin genetics, biosynthetic pathway and the mechanism underlying their mode of actions is required.

The DNA sequences of a large number of bacteriocin loci which are chromosomally encoded or plasmid-borne have been determined during the past decades by various workers (Dimov *et al.*, 2005; Chen and Hoover, 2003; Cintas *et al.*, 2001) to describe the genetic determinant of bacteriocin and the organisation of bacteriocin loci (Eijsink *et al.*, 2002). Biosynthesis of LAB bacteriocins was reported to encompass several genes, namely structural gene, immunity gene, regulatory genes and genes encoding a dedicated ABC-transporter and its accessory proteins. To date, the available scientific information demonstrated that bacteriocin genes are in close proximity to each other,

organized into operon structures and controlled by a specific regulatory system (Dimov *et al.*, 2005).

A number of bacteriocins produced by *Lactobacillus plantarum* (generally known as plantaricin) have been described (Smaoui *et al.*, 2010; Todorov *et al.*, 2007; Todorov and Dicks, 2005; Todorov and Dicks, 2004; Messi *et al.*, 2001). However, only a few plantaricin (*pln*; with italic formatted is used to describe gene) loci have been characterized genetically. The structure and organisation of the *pln* loci may be simple or complex. The relatively simple *pln* loci are *plW* locus encoding Class I two-peptide plantaricin W (Holo *et al.*, 2001), *plS* locus encoding Class IIb plantaricin S (Stephens *et al.*, 1998) and *pln423* locus encoding Class IIa plantaricin 423 (van Reenen *et al.*, 2003). The *plW*, *plS* and *pln423* loci are organised into one operon. Recently, many studies have been conducted for *plnEF* loci that were widely distributed among *L. plantarum* that could be isolated from various ecological niches. The well characterized *plnEF* locus have been reported for *L. plantarum* C11 (Diep *et al.*, 1996), WCFS1 (Kleerebezem *et al.*, 2003), JDM1 (Zhang *et al.*, 2009), J23 (Rojo-Bezares *et al.*, 2008), J51 (Navarro *et al.*, 2008), NC8 (Maldonado *et al.*, 2003) and V90 (Diep *et al.*, 2009). For simplicity, the reported *plnEF* loci was designated for the *plnEF* locus of *L. plantarum* JDM1, C11, WCFS1, V90, J51, NC8 and J23. The size of the reported *plnEF* loci are between 18-19 kb, displaying mosaic like structure with 22 to 26 genes that are organised into five to six operons. Together, the reported *plnEF* loci encoded a total number of four class IIb plantaricins and three regulatory networks (Diep *et al.*, 2009).

L. plantarum I-UL4 isolated from *tapai ubi* (fermented tapioca, a Malaysian traditional fermented food) exhibited a broad inhibitory spectrum against various Gram-positive (*Bacillus cereus*, *Staphylococcus aerues*, *Streptococcus pneumoniae*, *Enterococcus faecalis*, *Ent. faecium* and *Pediococcus acidilactici*) and Gram-negative bacteria (*Escherichia coli* and *Salmonella typhimurium*) (Lim, 2003). The probiotic effects of the bacteriocin-containing postbiotic metabolites produced by *L. plantarum* I-UL4 have been reported in rats and livestock animals (Loh *et al.*, 2010, 2009, 2008a; Thanh *et al.*, 2009; Foo *et al.*, 2003).

According to Moghadam *et al.* (2010), *L. plantarum* I-UL4 is a multi-bacteriocin producer that harbours two *pln* structural genes of *plW* and *plnEF*. The simultaneous occurrence of both *plW* and *plnEF* encode for plantaricin W and plantaricin EF respectively has not been reported elsewhere. Furthermore, the genetic loci harbouring *plnEF* is of high plasticity and possesses many variable regions with respect to their mosaic genetic composition and regulatory network. Hence the characterization of the *pln* loci is important as variations in gene sequence, gene composition and organisation will lead to different antimicrobial spectrum. Besides, new open reading frame (ORF) can be discovered in close proximity to known bacteriocin genes. Therefore, the objectives of this study were:

- a) To screen bacteriocin structural and biosynthetic genes in *L. plantarum* I-UL4.
- b) To determine the organisation of bacteriocin gene loci of *L. plantarum* I-UL4.
- c) To determine the genetic location of the bacteriocin gene loci.

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