UNIVERSITI PUTRA MALAYSIA

ISOLATION, MOLECULAR CHARACTERISATION AND BIOPROSPECTING OF ACTINOBACTERIA FROM GREENWICH ISLAND AND DEE ISLAND, ANTARCTICA

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By

CHU PEK LIM

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

ISOLATION, MOLECULAR CHARACTERISATION AND BIOPROSPECTING OF ACTINOBACTERIA FROM GREENWICH ISLAND AND DEE ISLAND, ANTARCTICA

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December 2014

Chair : Cheah Yoke Kqueen, PhD
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Antarctica is a pristine region on Earth that is well known for its extreme environmental conditions. The limited distribution of microbes shaped by the biogeography of Antarctica might promote the development of endemic microbial populations and evolution of endemic taxa with unique cold-adaptation and survival strategies in the harsh environment. *Actinobacteria* is one of the dominant soil inhabitants in the Antarctic continent. A total of 15 soil samples were collected from different sites of Greenwich Island and Dee Island to investigate the distributions of actinobacteria in the soil and to reveal their biosynthesis potential. Molecular screening for actinobacteria was achieved by amplifying the large insert stretch specifically found in the 23S rRNA gene of *Actinobacteria*. A selective isolation approach enabled 36 actinobacteria isolates of ten different genera to be successfully recovered. The highest diversity and abundance of actinobacteria was harboured in slightly alkaline soil (62.5%), compared to the moderately alkaline soil (26.8%) and extremely alkaline soil (10.7%). The major representatives of *Actinobacteria* belong to the genera *Streptomyces, Micrococcus, Kocuria and Micromonospora*. Phylogenetic analysis revealed that one presumptive new species of *Micromonospora* was isolated (98.8% 16S rRNA gene sequence similarity). Through the PCA analysis, water availability which serves as a dynamic source for the interactions of microbes was examined as the principal factor that shaped the distribution of actinobacteria from Greenwich Island and Dee Island. The presence of the biosynthetic systems polyketide synthase (PKS) and non-ribosomal peptide synthase (NRPS) in the genomes of the actinobacteria isolates indicated their great biosynthesis potential. In the expression analysis, the bioactive compounds recovered in ethyl acetate extracts were showing antibacterial activity against a broad spectrum of Gram-positive and Gram-negative pathogenic bacterial strains. The best group of antibacterial producers was the actinobacteria isolated from highly alkaline soil (>pH8.5), which exhibited 19.5% higher antibacterial activity than the next group of isolates from moderately alkaline soil (pH 7.9-8.4). The random amplified polymorphic DNA (RAPD) analysis was capable of detecting the intra-specific genetic variations among the 11 *Streptomyces* species and generated a specific cluster of *Streptomyces albidoflavus*. Other than taxonomic classification, RAPD is also capable of segregating the

actinobacteria isolates into clusters having specific antibacterial patterns. Antarctica has emerged as a natural reservoir of actinobacteria with great biosynthesis potential for bioprospecting.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia
Sebagai memenuhi keperluan untuk Ijazah Master Sains

PENGASINGAN, PENCIRIAN MOLEKUL DAN BIOPROSPEK ACTINOBACTERIA DARIPADA PULAU GREENWICH DAN PULAU DEE, ANTARTIKA

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Disember 2014

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Antartika merupakan satu kawasan yang asal di Bumi dan terkenal dengan keadaan persekitaran yang ekstrim. Taburan mikrob yang dihadkan oleh biogeografi Antartika mungkin menggalakkan pembentukan populasi mikrob yang endemik dalam alam sekitar yang sukar. *Actinobacteria* merupakan salah satu penghuni dominan dalam tanah benua Antartika. Sebanyak 15 sampel tanah telah dikumpulkan dari tempat-tempat yang berlainan di Pulau Greenwich dan Pulau Dee untuk menyiasat penaburan actinobacteria di dalam tanah dan mendedahkan potensi biosintesis actinobacteria tersebut. Pemeriksaan molekular untuk *actinobacteria* daripada pencilan bakteria telah dicapai dengan amplifikasi sisip besar khusus yang terdapat dalam gen 23S rRNA filum *Actinobacteria*. Kaedah pengasingan terpilih membolehkan 36 pencilan *actinobacteria* yang terdiri daripada sepuluh jenis genus yang berbeza telah berjaya diperolehi. Actinobacteria yang terbanyak dan berkepelbagaian tinggi adalah daripada tanah beralkali rendah (62.5%), berbanding dengan tanah beralkali sederhana (26.8%) dan beralkali ekstrim (10.7%). Wakil-wakil majoriti *Actinobacteria* adalah genus *Streptomyces*, *Micrococcus*, *Kocuria* dan *Micromonospora*. Analisis filogenetik mendedahkan bahawa satu spesies novel andaian daripada *Micromonospora* telah diasingkan, dengran rujukan kepada persamaan jujukan gen 16S rRNA. Melalui analisis PCA, air yang berfungsi sebagai sumber dinamik untuk interaksi mikrob telah dikaji sebagai faktor utama yang membentuk corak penaburan actinobacteria dari Pulau Greenwich dan Pulau Dee. Kehadiran sistem biosintetik poliketida sintase (PKS) dan Peptida Nonribosom (NRPS) dalam genom pencilan *actinobacteria* mendedahkan potensi biosintesis yang tinggi. Dalam analisis ekspresi, komposisi bioaktif dalam ekstrak etil asetat menunjuk aktiviti antibakteria terhadap patogen-patogen bakteria Gram-positif dan Gram-negatif yang berspektrum luas. Kumpulan terbaik penghasilan antibakteria adalah *actinobacteria* daripada tanah beralkali tinggi (> pH 8.5), dengan menunjukkan aktiviti antibakteria sebanyak 19.5% lebih tinggi daripada kumpulan yang berikutnya, iaitu actinobacteria daripada tanah beralkali sederhana (pH 7,9-8,4). Analisis *Random Amplification of Polymorphic DNA* (*RAPD*) dapat mengesan variasi genetik intra-spesifik antara 11 spesies *Streptomyces* dan menjana kelompok tertentu *Streptomyces albidoflavus*. Selain daripada pengelasan taksonomi, *RAPD* juga mampu

mengasingkan pencilan *actinobacteria* ke dalam kelompok corak antibakteria tertentu. Antartika muncul sebagai takungan semula jadi *actinobacteria* yang memiliki potensi tinggi dalam biosintesis bagi tujuan bioprospek.

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I certify that a Thesis Examination Committee has met on 17 December 2014 to conduct the final examination of Chu Pek Lim on his thesis entitled "Isolation, Molecular Characterisation and Bioprospecting of Actinobacteria from Greenwich Island and Dee Island, Antarctica" 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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The thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Master. The members of the Supervisory Committee were as follows:

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LIST OF SYMBOLS, UNITS, ABBREVIATIONS AND TERMS

%	percentage
℃	degree Celcius
rpm	revolution per minute
w/v	weight/volume
RNA	ribonucleic acid
DNA	deoxyribonucleic acid
rRNA	ribosomal RNA
PCR	polymerase chain reaction
RFLP	restriction fragment length polymorphism
RAPD	Random Amplification of Polymorphic DNA
CLPP	community level physiological profile
PLFA	phospholipid fatty acid analysis
PCA	Principal Component Analysis
NGS	Next-Generation Sequencing
MRSA	methicillin-resistant *Staphylococcus aureus*
LGT	lateral gene transfer
BLAST	Basic Local Alignment Search Tool
SDS	sodium dodecyl sulphate
dNTP	dinucleotide triphosphate
pH	potential of hydrogen
PKS	polyketide synthase
KS	ketosynthase
NRPS	non-ribosomal peptide synthase
UV	ultraviolet
TE	tris-ethylenediamine tetraacetate
CFCS	cell-free culture supernatant
DMSO	dimethyl sulfoxide
ISP	International *Streptomyces* Project
CFU	colony forming unit
UPGMA	unweighted paired group method with arithmetic mean
PUFA	polyunsaturated fatty acids
AFP	antifreeze protein

CHAPTER 1

INTRODUCTION

Soil is an essential and principal component on Earth, in which it could harbor the most diverse and complicated biological sources. Microbial communities have found to be closely related and perform around 80-90% of the biological events in the soils (Nannipieri & Badalucco, 2003). One gram of soil could harbour 6000 bacterial genomes, reflecting the great diversity of microbes that inhabited and probably can be isolated from the soils (Torsvik et al., 1996). However, the distribution of soil microbes still remains unclear, either they are widely distributed or geographically native. Through the molecular approaches that applied in the study of microbial ecology, somehow the distance and historical and contemporary environmental conditions have found to be some of the conclusive factors that shaped the biogeographic structure of bacteria (Martiny et al., 2006). In this study, the ordination method such as principal component analysis (PCA) is used to access the environmental factors that underlie the distribution of actinobacteria from Greenwich Island and Dee Island, Antarctica.

Secondary metabolites are low molecular weight organic substances produced by various living things, included microbes (Davies & Ryan, 2012). The interest of study has gained on the potential biological activities of these natural products secreted by microbes, included bacteria and fungi. Nevertheless, these microbial metabolites are only being synthesised upon certain stage of growth. Therefore, actinobacteria of this study are grown on solid agar (primary screening) and culture media broth (secondary screening) to access their secondary metabolites production in different growth conditions.

Actinobacteria is one of the dominant soil inhabitants. Presently, the phylum *Actinobacteria* comprised of more than 300 genera, representing one of the largest phyla within the domain *Bacteria* (Gao & Gupta, 2012). In line with this, the genus *Streptomyces* is the most studied group and also recognised as the most prolific producer of bioactive secondary metabolites (Berdy, 2005). Low discriminatory power of phenotypic morphological and chemotaxonomic profiles up-to-date has make it difficult for us to understand the taxonomy and evolutionary of *Actinobacteria* (Embley & Stackebrandt, 1994). On the basis of ribosomal RNA (rRNA) sequences comparisons as advocated by Woese, the evolution of *Actinobacteria* had been studied extensively to uncover their interrelationship. The 16S rRNA gene is commonly presented in prokaryotes and is highly conserved. This gene serves as a molecular signature for the classification of actinobacteria isolates.

Over the past decades, polymerase chain reaction (PCR) has become more accessible and widely applied in laboratory research (Erlich, 1989). With the advance development in molecular biology techniques, many useful genome mapping assays have been developed by implementing the PCR technique, such as random amplified polymorphism DNA (RAPD) (Welsh & McClelland, 1990). DNA polymorphism analysis by RAPD methods enables the differentiation of closely related bacterial strains within species level. Apart from that, RAPD is capable of revealing the relationships

between actinobacteria isolates, such as antibacterial profile, in accordance to their genetic diversity.

Recently, the increased emergence of multiple-drug resistance pathogens has brought to a serious impact on the therapeutic of pathogen-causing infections and diseases (Demain & Sanchez, 2009). Antibiotic resistance was declared by World Health Organisation (WHO) as a rapidly evolving health issue and a threat to global health security in May2013. A high percentage of hospital-acquired infections are caused by highly resistant bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin or multidrug-resistant enterococci Gram-negative bacteria (Annual report on the antibiotic resistance monitoring/surveillance network, 2008). This, followed by the rapid declined effectiveness of the existing antibiotics, applied for the treatment of pathogen infections. During the search for bioactive compounds, the situation become even worse when well-known compounds are being produced by different microbes that are isolated from various environments (Bredholt et al., 2007). Notably, the search and discovery of novel and new generations or classes of drugs from microbes, especially actinobacteria from poorly explored area, the Antarctica, has seemed to be the potent alternative of relieving the current crisis.

Antarctica, one of the polar regions, and also a poorly explored area on Earth by humans, now emerged as a new hope for the discovery of novel bacterial species and isolation of novel bioactive secondary metabolites (Smith et al., 2006; Teixeira et al., 2010; Li et al., 2011; Muñoz et al., 2011; Wong et al., 2011; Gesheva & Negoita, 2012; Lee et al., 2012). The harsh environment and extreme conditions on this pristine continent have contributed to the evolution of bacteria by acquiring unique cold-adaptation and survival strategies (Teixeira et al., 2010). By taking the initiative of isolating rare species of *Actinobacteria* from this continent, it will greatly improve our understanding regarding their distribution, ecological and evolutionary relationship in Antarctica and their unique biosynthesis potential.

Objectives of the study

The study was undertaken with the following objectives:

1. To isolate and identify the different genera of *Actinobacteria* from soil samples from Greenwich Island and Dee Island, Antarctica.
2. To characterise the selected actinobacteria isolates through DNA profile by using RAPD fingerprinting method.
3. To investigate the biosynthesis potential of actinobacteria isolates by using PCR method and expression-based method.

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