UNIVERSITI PUTRA MALAYSIA

CHARACTERIZATION OF PEPTIDES AND PROTEINS FROM EPIDERMAL MUCUS OF CLIMBING PERCH Anabas testudineus (Bloch, 1972) WITH ANTIBACTERIAL AND IMMUNOMODULATORY PROPERTIES

AGHARID ALI HUSSEIN

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By

AGHARID ALI HUSSEIN

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

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DEDICATION

In the name of Allah, the most compassionate, the most merciful

In memory of my beloved parents, who unconditionally supported me throughout my academic career. Though they are no longer with me physically, their love was ever-present, and I have fulfilled their aspirations for me. May Allah (swt) reunite us in Paradise

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

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Chairman : Associate Professor Hassan Hj Mohd Daud, PhD
Faculty : Veterinary Medicine

The skin of fish with its large mucosal surface contains a variety of biologically active compounds and antimicrobial peptides that are constitutively expressed to provide protection against potential pathogenic microbes. Climbing perch (*Anabas testudineus*) is an obligate air breather and tolerates extremely unfavourable water conditions. Its body is covered by a thick coat of mucus composed of mucopolysaccharides, lipids and proteins making the fish a suitable candidate to obtain bioactive compounds such as antibacterial proteins and peptides. Based on this background, the assessment of the antimicrobial and immunomodulatory effects of bioactive proteins and peptides in crude mucous extracts derived from epidermis of the climbing perch is an important step. Hence, the aim of this study was to determine the antimicrobial and immunomodulatory effects of the bioactive crude mucous extract from epidermis of climbing perch in order to test their efficacy both *in vivo* and *in vitro*.

The bioactive crude mucous extract was prepared in aqueous and acidified form by heating moderately, followed by assessing their immune components as well as evaluating their antibacterial activity and determining some immune-related enzymes using well agar diffusion test, respectively. Proteomic analysis was also conducted to estimate the protein concentration including SDS-PAGE, haemolytic activity of the acidic crude extract as well as histopathological analysis. The minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) as well as $NaCl_2$ tolerance of the bioactive crude were also conducted. Antibacterial activity was found to be statistically significant ($P<0.05$) showing maximum activity against *P. aeruginosa* ATCC10145. However, no haemolytic

activity was observed for the acidified crude extract on horse RBCs. Total soluble protein concentration by OPA assay and SDS-PAGE profile revealed 13 bands (245-11 kDa) distinguished using NuPAGE 4-12% Bis-Tris (Novex Invitrogen) gel. The MIC and MBC of mucous crude extract as determined by resazurin-based microliter dilution assay was found to have a similar value (2.5mg/ml) against multidrug resistance (MDR) *P. aeruginosa* ATCC10145 in addition to salt tolerance at physiological solution. Assessment of the immune-related enzymes activities of protease, lysozyme and esterase in bioactive crude indicated significant roles in disease defence mechanism. Similarly, antimicrobial proteins and peptides isolated by sepPak C18 and Ultrafiltration 30kDa and Superdex™peptide showed that the fractions in the first peak refer to antibacterial properties against *P. aeruginosa* ATCC 10145. Furthermore, bioactive fractions were run through Q-TOFLC/MS with subsequent digestion by trypsin to identify the antimicrobial proteins and peptides. This was the first time to identify novel ApolipoproteinA-1 (Antimicrobial proteins) and Haemoglobin subunit beta (Fragment) as well as β-actin (Fragment) and Elongation factor 1-α (Fragment) and Cytochrome-C oxidase subunit1(Fragment) in mucous crude extract derived from epidermal scraping of climbing perch. The *de novo* peptide AAGPKGPLGPR was selected among other *de novo* peptides as it was predicted to be antibacterial peptide according on its net charge (+2), low residues (11), the hydrophobic ratio of 27% and richness in proline and glycine. Following the proteomic analysis of bioactive crude and estimation of immune related enzymes activities, the efficacy of antimicrobial proteins and bioactive potential peptide in the crude (AMPPC) against *P. aeruginosa* ATCC 10145 was applied in an animal model. The inoculum size for MDR of *P. aeruginosa* ATCC 1014 was determined at 2×10^7 CFU/mouse using Reed and Muench method and oral administration AMPPC at 6.38mg/mouse was nontoxic to male ICR mice, with no change in physical state and body weight as compared to the control group, PBS only. Moreover, liver function enzymes, ALT and AST were not significantly different when compared to the control group mice given PBS only. In addition, kidney function indicator, creatinine and urea levels revealed no significant difference. Histological examination of liver and kidney manifested normal histological architectures. The efficacy test of AMPPC showed that mice injected with 2×10^7CFU/mouse of *P. aeruginosa* ATCC 10145 in 0.2 ml of AMPPC, CE and PBS solutions and evaluated after 48 hrs, indicated there were significant decreased ($P<0.05$) in mortality rate and bacteria count in organs and blood samples, liver enzymes (AST and ALT), renal functions (creatinine and urea levels) and pro-inflammatory cytokines TNF-α and IL-6 in treatment groups by bioactive crude mucous extract, as compared to non-treatment and antibiotic treatment groups.

In conclusion, the epidermal mucous of the climbing perch are natural sources of antimicrobial proteins and peptides. Similarly, the proteomic analysis of bioactive crude extracts derived from the epidermal mucous may serve as an opening to further investigations to determine their potential medical application as antibacterial agent for preventing and elimination of *P. aeruginosa* sepsis.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Doktor Falsafah

PENCIRIAN PEPTID DAN PROTEIN DARI MUKUS EPIDERMAL IKAN PUYU, *Anabas testudineus* YANG BERSIFAT ANTIBAKTERIA DAN IMUNOMODULATORI

Oleh

AGHARID ALI HUSSEIN

April 2018

Pengerusi : Profesor Madya Hassan Hj Mohd Daud, PhD
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Kulit ikan mempunyai permukaan lapisan mukosa yang luas mengandungi pelbagai sebatian biologikal aktif serta peptid antimikrob yang terungkap berurutan untuk memberi perlindungan terhadap mikrob berpotensi patogenik. Ikan puyu (*Anabas testudineus*) adalah ikan obligat sedutan udara dan tahan keadaan air tidak sesuai yang ekstrem. Badannya diseliputi oleh lapisan tebal mukus terdiri daripada mukopolisakarida, lipid dan protein yang menjadikan ikan tersebut calon yang sesuai untuk mendapatkan sebatian bioaktif seperti protein antibakteria dan peptid. Berdasarkan latarbelakang ini penilaian terhadap kesan antimikrob dan imunomodulatori bioaktif protein dan peptid dalam ekstrak kasar terbit dari epidermis ikan puyu adalah satu langkah yang penting. Olehitu tujuan kajian ini adalah untuk menentukan kesan antimikrob dan imunomodulatori ekstrak bioaktif mukus mentah dari epidermis ikan puyu untuk menguji keberkesanan dalam *in vivo* dan *in vitro*.

Ekstrak bioaktif mukus kasar telah disediakan dalam bentuk akuas dan terasid dengan memanaskan secara sederhana, diikuti masing-masing dengan penilaian komponen imun dan penilaian aktiviti antibakteria dan menentukan beberapa enzim berkait dengan keimunan menggunakan ujian resapan gel agar-agar. Analisis proteomik juga dijalankan untuk menganggarkan kepekatan protein seperti SDS-PAGE, aktiviti hemolitik ekstrak berasid mentah dan juga analisis histopatologikal. Ujian kepekatan perencat minimal (MIC) dan kepekatan bakterisidal minimal (MBC) dan ujian tolerans $NaCl_2$ juga dijalankan. Ujian antibakteria menunjukkan aktiviti maksima terhadap *Pseudomonas aeruginosa* ATCC10145 dengan statistik yang bererti ($p<0.05$). Walaubagaimana pun tiada aktiviti hemolisis untuk ekstrak terasid kasar terhadap sel darah merah kuda. Kepekatan protein total terlarut melalui

asei OPA dan profil SDS-PAGE menunjukkan 13 jalur (11-245 kDa) berbeza menggunakan NuPAGE 4-12% gel Bis-Tris (Novex Invitrogen). Nilai MIC dan MBC ekstrak mukus kasar sebagaimana ditentukan dengan asei larutan mikroliter berdasar resazurin menunjukkan nilai yang serupa (2.5 mg/ml), terhadap kerintangan multidrug (MDR) *P. aeruginosa* ATCC10145, tambahan kepada toleransi terhadap garam dalam larutan fisiologi. Penilaian enzim berkait imun menunjukkan nilai-nilai berert dalam protease, lisozim dan esterase yang mana menandakan peranan mereka dalam mekanisma ketahanan penyakit. Dalam keadaan yang sama protein dan peptid antimikrob yang dipencil dengan sePak C18, pengultraemparan 30kDa dan Superdex^{TM}peptide menunjukkan fraksi dalam puncak pertama merujuk pada sifat antibakteria terhadap *P. aeruginosa* ATCC 10145. Tambahan lagi, fraksi bioaktif diuji melalui Q-TOFLC/MS dan diikuti oleh pencernaan dengan tripsin bagi mengenalpasti protein dan peptid antimikrob. Ini adalah kali pertama langkah mengenalpasti ApolipoproteinA-1 yang novel (protein antimikrob), β-haemoglobin subunit (fragmen), β-actin (fragmen), faktor pemanjangan 1-α (fragmen) dan juga sitokrom-C oksidase (fragmen) dalam ekstrak kasar mukus dari kikisan epidermal ikan puyu. Peptid *de novo* AAGPKGPLGPR telah dipilih dari peptid *de novo* yang lain kerana ianya diramal sebagai peptid antibakteria mengikut cas bersih (+2), residu rendah (11), nisbah hidrofobik bernilai 27% dan kaya dengan prolina dan glisina. Selepas analisis proteomik ekstrak bioaktif kasar dan anggaran aktiviti enzim berkait keimunan, keberkesanan protein antimikrob dan potensi bioaktif peptid (AMPPC) dalam ekstrak kasar terhadap *P. aeruginosa* ATCC 10145 dijalankan dalam model haiwan. Saiz inokulum untuk MDR P. *aeruginosa* ATCC 10145 ditentukan pada 2x107 CFU/mencit menggunakan kaedah Reed dan Muench. Pemberian oral AMPPC pada 6.38mg/mencit adalah tidak toksid terhadap mencit ICR jantan, dengan tiada perubahan keadaan fizikal dan berat badan sebagaimana dibandingkan dengan kumpulan kawalan iaitu PBS sahaja. Juga enzim fungsi hepar, ALT dan AST tidak menunjukkan perubahan bererti apabila dibandingkan dengan kumpulan mencit kawalan yang diberi PBS sahaja. Tambahan lagi penunjuk fungsi ginjal iaitu paras kreatinina dan urea menunjukkan tiada berbezaan bererti. n Pemeriksaan histologi hepar dan ginjal mempamerkan arkitektur yang normal. Ujian keberkesanan AMPPC menunjukkan mencit yang disuntik dengan $2x10^7$ CFU/mencit *P. aeruginosa* ATCC 10145 dalam 0.2 ml of larutan AMPPC, CE dan PBS dan dinilai selepas 48 jam, menunjukkan terdapat penurunan bererti ($P<0.05$) dalam kadar mortaliti dan bilangan bakteria dalam sampel organ dan darah, enzim hepar (AST dan ALT), fungsi ginjal (paras kreatinina dan urea) dan pro-inflamatori sitokin TNF-α dan IL-6 dalam kumpulan dirawat dengan ekstrak kasar bioaktif mukus apabila dibanding dengan kumpulan tanpa rawatan dan dirawat dengan antibiotik.

Akhir kata, mukus dari epidermal ikan puyu adalah sumber asli protein dan peptid antimikrob. Secara yang serupa analisis proteomik ekstrak bioaktif kasar dari mukus epidermal boleh bertindak sebagai ruang untuk sisatan lanjut untuk menentukan kegunaan perubatan sebagai agen antibakteria bagi mengelak dan menyingkir sepsis *P. aeruginosa*.

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I certify that a Thesis Examination Committee has met on 20 April 2018 to conduct the final examination of Agharid Ali Hussein on her thesis entitled "Characterization of Peptides and Proteins from Epidermal Mucus of Climbing Perch *Anabas testudineus* (Bloch, 1792) with Antibacterial and Immunomodulatory Properties" 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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This thesis was submitted to the Senate of the Universiti Putra Malaysia and has been accepted as fulfillment of the requirement for the degree of Doctor of Philosophy. The members of the Supervisory Committee were as follows:

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I hereby confirm that:

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This is to confirm that:

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Name of Member of Supervisory Committee: Dr. Farina Mustaffa Kamal

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ALT	Alanine Aminotransferase
ALP	Alkaline phosphatase
AMPs	Antimicrobial peptides and proteins
AMPP	Antimicrobial peptides and proteins
AMPPC	Antimicrobial proteins and bioactive potential peptide in the crude
APOL1	Apolipoprotein L1
AST	Aspartate Aminotransferase
ACE	acidic crude extract
BC	bioactive crude
BCE	bioactive crude extract
ACN	Acetonitrile
BHI	Heart Infusion Broth
BSA	Bovine Serum Albumin
BSI	bloodstream infections
CE	Ciprofloxacin
°C	Degree Celsius
CF	Cystic fibrosis
CFU	Colony Form Unit
CLSI	Clinical and Laboratory Standards Institute
DMSO	Dimethyl sulfoxide
D.W	Distilled Water
EML	Epidermal mucus and Epidermis Layer
HAc	Acetic acid
H&E	Harris'haematoxylin
HDAPs	Histone-derived antimicrobial peptides
h	hour
IACUC	Institutional Animal Care and Use Committee recommendations

IL-6	Interleukin-6
IL-8	Interleukin-8
IL-1b	Interleukin-1b
I	Intermediate sensitive
IP	Intraperitoneal
IZD	Inhibition Zone Diameter
IgA	Immunoglobulin A
IgG	Immunoglobulin G
kDa	Kilo Dalton
LC/MS	Liquid Chromatography–Mass Spectrometry
LPS	lipopolysaccharides
LYZ	Lysozyme
MAR	Multiple antibiotic resistance index
MBC	Minimal Bactericidal Concentration
MDR	Multidrug-resistant
Me	Meropenem
MHA	Muller–Hinton agar
MIC	Minimal Inhibitory Concentration
ml	Milliliter
µl	Microliter
mg	milligram
µg	Microgram
mm	Millimeter
mM	Millmole
µmole	Micromole
MRSA	Methicillin Resistant S. aureus
Mwt	Molecular weight
PBS	Phosphate Buffered Saline
PAMP	pathogen-associated molecular pattern
PA	Pseudomonas aeruginosa

pg.	Pictogram
PG-1	Protegrin-1
PIS	Pathological Inflammation scoring
p-NP	p-nitrophenol
p-NNP	p-nitrophenylphosphate
O.D	Optical Density
OPA	O-Phthaldialdehyde
RBCs	Red Blood Cells
Rf	Relative mobility
R	Resistant
R2	linear regression
S	Sensitive
S.D	Standard deviation
SEC	Size exclusion chromatography
SDS–PAGE	Sodium dodecyl sulfate-polyacrylamide gel electrophoresis
TFA	Trifluoroacetic acid
TNF-α	tumor necrosis factor-α
T2SS	Type II Secretion System
T3SS	Type III Secretion System

CHAPTER 1

INTRODUCTION

Bioprospecting is an organized search to find beneficial products obtained from bioresources including plants, microorganisms and animals, that use in creating and investigating new biological compounds with medicinal and commercial values for health purposes (Oyemitan,2017).The evolution and adaptation by animals that allow them to survive under extreme environmental conditions are the result of developed functions that may have resulted from acquiring traits and features containing essential bioactive components. Whenever these interesting bioactivities are found and the bioactive compounds can be isolated and identified, valuable new biological products can be developed (Chalamaiah *et al*., 2012; Harnedy and FitzGerald 2012). Common antibiotics and other chemical-based medicines are the most widely used ways to control bacterial infection in humans and animals (Salger et al., 2016). The widespread application of antibiotics has resulted in the emergence of resistant pathogens that are capable of withstanding the effect of commonly used antibiotics. Therefore, the world needs novel active biomolecules to combat the emerging and re-emerging pathogen that affect human health and aquatic lives (Manikantan et al., 2016). Active biomolecules are the components of the innate immune system (Salger et al., 2016). Antimicrobial peptides (AMPs) and other protein materials are produced by a large number of organisms and are essential components of the innate immune system (Costa *et al*., 2017; Salger *et al*., 2016 Zhang and Gallo, 2016). They are readily produced when the organisms are subjected to adverse environmental conditions (Costa *et al*., 2017; Zhang and Gallo, 2016). These small molecules have been shown to exhibit a broad spectrum of antimicrobial activities against many organisms including bacteria, yeasts, fungi, and viruses. They also possess significant anti-inflammatory and immunomodulatory activities as well as cytotoxic activity on cancer cells (Kang *et al*., 2017). Since the first AMP was described in humans, over 2700 kinds have been discovered in all life forms ranging from bacteria to human (Valero *et al*., 2013). The first AMP was discovered in 1922 and this has attracted researchers' attention since the 1980s (Wang, 2017).

The aquatic habitat is home to an array of organisms that have developed features and adaptations that permit them to live remarkably in these enclaves. Notable among the inhabitants of the aquatic ecosystem are fish. They have evolved ways to survive including possessing many biological components as well as bioactive defence system that serves to protect them from the load of bacteria present in water (Harnedy and FitzGerald, 2012). The protection is conferred by both specific and nonspecific immune components. One of the major components of the nonspecific defence mechanism in fish is the antimicrobial peptides and proteins. They are the major components of the fish's innate immune response to a wide range of opportunistic pathogens (Nsrelden *et al*., 2017). Morever, the immunological activity of AMPs, they also possess inflammatory and modulatory roles as part of their innate and adaptive immune responses, as well as act as chemokines to recruit other

effector cells (Cuesta *et al*., 20011; Chertov *et al*., 1996; Oppenheim *et al*., 2003; Kang *et al*., 2017).

The teleosteii taxon is made up of over 24,000 different species; hence, only small fractions of this taxon of fish species have been studied. The majority of these studies utilised them as experimental models in order to explore their commercial potentials to the aquaculture industry and about 62 different AMPs have been reported in many fish species (Smith and Fernandes, 2009; Valero *et al*., 2013). Peptides of fish origin are reportedly active in very harsh environmental conditions, including very high salt concentrations, making them suitable candidates for development of therapeutic antimicrobial agents (Masso-Silva and Diamond, 2014).

Anabas testudineus, commonly known as climbing perch, is an obligate air breather (Sayer,2005). The species represents an economically useful commodity and is a very good source of food in Southeast Asia especially in Thailand, Malaysia, and the Philippines (Chotipuntu *et al*., 2011; Loh *et al*., 2015). It is a euryhaline teleost, inhabiting both freshwater and brackish water ecosystems of Southeast Asian countries (Kohinoor *et al*., 1991; Sarkar *et al*., 2005) and is tolerant to extremely unfavourable water conditions and high salinity (Ip *et al.,* 2013; Khan *et al*., 1976; Sarkar and Ponniah, 2000). The body surface of *Anabas testudineus* is covered by a thick coat of mucus which is composed of mucopolysaccharides, lipids, and proteins. These substances are important in keeping the skin moist thereby facilitating the survival of the fish in harsh situations (Agarwal *et al*., 1980). The climbing perch has extraordinary tissue regeneration potential and this characteristic may have medical applications for skin regeneration (Srivastava *et al*., 2013). Therefore, the skin mucus of *Anabas tetudineus* is suitable for research material of bioactive compounds such as antibacterial proteins and peptides.

Natural antimicrobial proteins and peptides have the ability to kill microbes and antibiotic-resistant bacteria. Roughly all fish antimicrobial peptides and proteins (AMPPs) have antibacterial activities against several types of bacteria. Some of the fish AMPPs have the ability to act in high salt concentrations, make them perfect potential targets for development as therapeutic antimicrobials. Epidermal mucus from selected freshwater fish species is a potential source of novel antimicrobial agents against antibiotic-resistance microorganisms.

This research hypothesised that epidermal mucus of the climbing perch generates a large variety of antimicrobial proteins and peptides. It will be a new natural drug alternative to antibiotics and have immunomodulatory functions for treatment of resistant pathogenic bacteria.

The specific objectives of the present study are:

1. To isolate crude antimicrobial proteins and peptides from the epidermal mucus of the climbing perch
2. To investigate the antimicrobial activity, haemolytic activities, and NaCl tolerance of the crude antimicrobial proteins and peptides.
3. To isolate and characterise the crude antimicrobial proteins and peptides.
4. To evaluate the efficacy of the crude antimicrobial proteins and peptides against *Pseudomonas aeruginosa* infection in mice models *in vivo*.

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