UNIVERSITI PUTRA MALAYSIA

MECHANISM OF METHICILLIN-RESISTANT Staphylococcus aureus BIOFILM DEGRADATION BY BACTERIOPHAGES

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By

KHULOOD HAMID DAKHEEL

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

January 2018

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DEDICATION

To

My children and my husband they are my inspiration and joy they gave me the strength I needed to finish this thesis

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

MECHANISM OF METHICILLIN-RESISTANT *Staphylococcus aureus* BIOFILM DEGRADATION BY BACTERIOPHAGES

By

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January 2018

Chairman : Professor Datin Paduka Khatijah Mohamad Yusoff, PhD
Faculty : Biotechnology and Biomolecular Sciences

Methicillin resistant *Staphylococcus aureus* (MRSA) is a persistent pathogen responsible for widespread nosocomial infections. A major virulence factor that confers both antimicrobial resistance and pathogenicity is the ability to form protective biofilms that protect the bacterial from the extracellular environment. Biofilms largely render antibiotics and host immune responses ineffective; and are implicated in nearly 80% of all chronic recurring infections. Emerging antibiotic resistance levels in bacteria are becoming an increasingly serious threat to global public health and impact the cost of health care for infectious diseases. Effective action plan and novel antimicrobials are needed to combat the global spread of MRSA. Potential novel antimicrobials are as bacteriophages (bacterial viruses or phages) that have natural predatory antimicrobial potency towards pathogenic bacteria. Although such viruses exist, little is known about predatory antimicrobial mechanisms of these phages in the control of bacterial populations within the biofilm.

This study has investigated the potential for phages to be used to target methicillin-resistant *S. aureus* biofilm producers. For this work, MRSA strains were isolated genotypically characterized based on the *Staphylococcal* protein A gene (*spa* type) and on biofilm formation. The proteins, exopolysaccharides, extracellular DNA and RNA within the biofilms were evaluated using a biofilm dispersal assay. Additionally, the packed-beads and mechanical disruption process assay were used to characterise the cell-surface adhesions and cohesion, respectively. The data showed that the predominant genotype (22 out of 25 isolates) was the *spa* type t127. The majority of the isolates were categorized as moderate biofilm producers. The dispersal assay showed that the polysaccharide intercellular adhesin (PIA)-independent mechanism was found in 12 and the remaining 13 isolates were PIA-dependent. Strong biofilm dispersal following (1) RNase and (2) DNase followed by proteinase K treatment was observed for both groups. Differences in dispersal between the isolates with the

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different mechanisms were seen. However; sodium metaperiodate caused dispersal in PIA-dependent biofilm wheres it stimulated biofilm formation of PIA-independent biofilms. Consequently, the amount of biofilm components and the adhesion and cohesion ability of the bacteria were non-correlated. In some isolates, the biofilm weakened the ability of the cells to adhere onto surfaces but strengthened cell-to-cell cohesion. The efficiency of these isolates to adhere onto glass beads increased after partial removal of the biofilm. It was concluded that nucleic acid and proteins are main components of biofilm matrix of MRSA clone t127 with observed relationship between adhesion and cohesion for biofilm tested. Secondly, promising phage candidates that target the MRSA biofilms were isolated from polluted water. Two phages, UPMK_1 and UPMK_2, were characterized based on one step growth curves, host infectivity, electron microscopy and genome diversity. The phages demonstrated antagonistic infectivity on planktonic cultures. This was further assayed using an *in vitro* static biofilm assay in microtiter-plates and *in vitro* visualization of the biofilm architecture *in situ* by labeling biofilm with two fluorescent stains, SYTO 9 and propidium iodide then performing confocal laser scanning microscopy (CLSM) analysis. Both phages produce halos around the clear zone of lysis on lawns of their specific host. The burst size was 32 PFU/cell for UPMK_1 and 67 PFU/cell for UPMK_2. Host specificity was determined on 25 biofilm producing MRSA. UPMK_1 and phage UPMK_2 can lyse all strains tested. Additionally, phage UPMK_2 can lyse another 25 strain belonging to MRSA ST239; a dominant MRSA strain in Far East countries including Malaysia. Morphologically, phage UPMK_1 is a *siphovirus* with 55.5 ± 1.5 nm head diameter and 335.9 ± 30.5 nm tail length with diameter 12.8± 1.5 nm. Phage UPMK_2 is a structurally large *podovirus* with a 110.5±59.8 nm head diameter and 28.3 ± 15.5 nm tail length. UPMK_1 has a genome size of 152788 bp with 155 predicted genes and UPMK_2 has 40955 bp with 62 predicted genes. Biofilm analyses and CLSM revealed that UPMK_1 and UPMK_2 degraded the biofilm after 6 hours and 8 hours, respectively. Phage protein profiles were determined as was the ability of phages to lyse the biofilms based on zymograpic analysis. Phage-host interaction were examined by 2DE protein profiles assessed using a matrix-assisted laser desorption ionization-time-of-flight (MALDI-TOF/TOF) mass spectrometer. In zymogram gels lytic activity for phage UPMK_1 and UPMK_2 on MRSA t127/4 and MRSA t223/20 biofilms, respectively, can be clearly observed. UPMK_2 is most effective as evidenced by four lytic bands compared to UPMK_1 that has a single lytic band. Mass spectrometry analysis for both UPMK_1 and UPMK_2 revealed that each band contains many peptides from several phage proteins. Furthermore, peptides with peptidase activity were predominant. Additionally, it was established that the biofilm lytic proteins in phage UPMK_2 also have lytic activity towards PIA-dependent and independent biofilm of others MRSA biofilm producers whereas UPMK_1 can only lyse its host. MS/MS analysis of the proteins in the biofilms induced in bacteria after phage treatments revealed that the phage infections up-regulated several metabolic pathways including those involved in energy conversion, protein metabolism, nucleotide metabolism and pathways involved in the generation of oxidants and antioxidants. This suggests they are firmly involved in the biofilm degradation. This study has provided significant amount of novel data to address fundamental questions about the biology of MRSA biofilm degradation by phages. It is envisaged that this data will be useful in the development of novel and effective therapeutic for control of the MRSA biofilms.

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

MEKANISME DEGRADASI BIOFLIM TAHAN-MRTHICILLIN *Staphylococcus aureus* SECARA TERAPI PHAGE

Oleh

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Januari 2018

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"Methicillin-resistant *Staphylococcus aureus*" (MRSA) merupakan patogen berterusan yang menyebabkan jangkitan nosokomial yang berleluasa. Faktor virulensi utama yang memberikan rintangan antimikrob dan patogenisiti adalah keupayaan untuk membentuk biofilm perlindungan yang melindungi bakteria daripada persekitaran ekstrasel. Sebahagian besar dari biofilm menyebabkan tindak balas terhadap antibiotik dan dengan itu mengurangkan keberkesanan perumah imun. Keadaan ini melibatkan hampir 80% daripada semua jangkitan berulang yang kronik. Tahap rintangan antibiotik yang muncul pada bakteria menjadi ancaman yang semakin serius terhadap kesihatan awam global dan meningkatkan secara mendadak kos penjagaan kesihatan untuk penyakit berjangkit. Pelan tindakan yang berkesan dan antimikrobial yang baru diperlukan untuk mengatasi penyebaran global MRSA. Antimikrobial baru yang berpotensi adalah sebagai bakteriofaj (virus bakteria atau faj) yang mempunyai potensi antimikrobial pemangsa semulajadi terhadap bakteria patogen. Walaupun virus tersebut wujud, hanya sedikit maklumat diketahui mengenai mekanisme antimikrob faj dalam mengawal populasi bakteria yang mempunyai biofilm. Kajian ini telah meneliti potensi faj untuk digunakan bagi mensasarkan pengeluaran biofilm MRSA. Dalam kajian ini, beban MRSA diasingkan secara genotip berdasarkan gen protein Staphylococcal A (jenis spa) dan pembentukan biofilm. Protein, eksopolisakarida, DNA ekstrasel dan RNA dalam biofilm dinilai menggunakan ujian penyebaran biofilm. Di samping itu, manik yang selubungi dengan tepu yang padat dan ujian proses gangguan mekanikal telah digunakan untuk mencirikan perekatan dan kepaduan pada permukaan sel. Hasil kajian menunjukkan bahawa sebahagian besar genotip (22 daripada 25 pengasingan) adalah jenis t127 spa. Majoriti isolat dikategorikan sebagai pengeluar biofilm yang sederhana. Pengujian penyebaran menunjukkan bahawa perekatan antara sel polisakarida (PIA) – mekanisme bebas ditemukan pada 12 dan selebihnya 13 isolat bergantung kepada PIA. Penyebaran biofilm yang kuat diikuti (1) RNase dan (2) DNase diikuti oleh rawatan proteinase K dapat diperhatikan untuk kedua-dua kumpulan. Terdapat juga perbezaan

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penyebaran antara isolat dengan mekanisme yang berbeza. Walau bagaimanapun, natrium metaperiodat menyebabkan penyebaran dalam biofilem yang bergantung kepada PIA yang mana ia merangsang pembentukan biofilm yang tidak bergantung pada PIA. Akibatnya, jumlah komponen biofilm dan keupayaan melekat dan kepaduan bakteria tidak berkorelasi. Dalam sesetengah isolat, biofilm melemahkan keupayaan sel untuk mengikuti permukaan tetapi memperkuat kepaduan sel antara sel. Kecekapan isolat ini untuk melekat pada manik kaca meningkat selepas penyingkiran sebahagian daripada biofilm. Dengan itu, dapat disimpulkan bahawa asid nukleik dan protein merupakan komponen utama matriks biofilm MRSA klon t127 melalui satu hubungan yang berkait diantara kebolehan untuk menjadi kohesif dan melekat biofilm yang diuji. Kedua, calon faj yang mensasarkan biofilm MRSA telah diasingkan dari air yang tercemar. Dua faj, UPMK_1 dan UPMK_2, dicirikan berdasarkan dari satu lengkung langkah pertumbuhan, jangkitan hos, mikroskopi elektron dan kepelbagaian genom. Faj menunjukkan keengganan antagonistik pada kultur planktonik. Ini diuji dengan menggunakan ujian biofilm statik secara *in vitro* dalam piring mikrotiter dan visual *in vitro* dalam seni bina biofilm *in situ* dengan melabel biofilm dengan dua noda pendarfluor, SYTO 9 dan propidium iodide kemudian melakukan analisis mikroskop pengimbasan laser konfokal (CLSM). Kedua-dua fasa menghasilkan zon lisis yang jelas di atas laman dari hos mereka yang spesifik. Saiz lisis ialah 32 PFU / sel untuk UPMK_1 dan 67 PFU / sel untuk UPMK_2. Perumah yang spesifik ditentukan pada 25 biofilm yang menghasilkan MRSA. UPMK_1 dan faj UPMK_2 boleh melisiskan semua strain yang diuji. Di samping itu, faj UPMK_2 boleh melisiskan lagi 25 strain yang dimiliki oleh MRSA ST239; strain MRSA yang dominan di negara-negara asia termasuk Malaysia. Berdasarkan morfologi, faj UPMK_1 adalah *Siphovirus* dengan diameter kepala 55.5 ± 1.5 nm dan panjang ekor 335.9 ± 30.5 nm dengan diameter 12.8 ± 1.5 nm. Faj UPMK_2 adalah *Podovirus* yang mempunyai struktur yang besar dengan diameter kepala 110.5 ± 59.8 nm dan panjang ekor 28.3 ± 15.5 nm. UPMK_1 mempunyai saiz genom 152788 bp dengan 155 gen yang diramalkan dan UPMK_2 mempunyai 40955 bp dengan 62 gen yang diramalkan. Analisis biofilm dan CLSM mendedahkan UPMK_1 dan UPMK_2 boleh merosakkan biofilm selepas masing-masing 6 jam dan 8 jam. Profil protein faj ditentukan seperti keupayaan faj untuk melisis biofilm berdasarkan analisis zimografi. Pemeriksaan Interaksi hos faj dilakukan melalui profil protein 2DE yang dinilai menggunakan spektrometer jisim ionization-time-of-flight (MALDI-TOF / TOF) yang dibantu matriks. Dalam zimogram gel aktiviti litik untuk faj UPMK_1 dan UPMK_2 pada MRSA t127/4 dan biofilm m MRSA t223/20, masing-masing, boleh dilihat dengan jelas. UPMK_2 adalah paling berkesan seperti yang dibuktikan oleh empat jalur litik berbanding dengan UPMK_1 yang mempunyai jalur litik tunggal. Analisis spektrometri jisim untuk UPMK_1 dan UPMK_2 mendedahkan bahawa setiap kumpulan mengandungi banyak peptida dari beberapa protein faj. Tambahan pula, peptida dengan aktiviti peptidase adalah dominan dan protein biofilem litik dalam faj UPMK_2 juga mempunyai aktiviti litik terhadap biofilm yang bergantung kepada PIA dan biofilm yang tidak bergantung kepada PIA daripada pengeluar biofilm MRSA yang mana UPMK_1 hanya boleh melisis perumahnya. Analisis MS / MS protein dalam biofilm selepas rawatan faj mendedahkan bahawa jangkitan faj dikawal melalui beberapa laluan metabolik termasuk yang terlibat dalam penukaran tenaga, metabolisme protein, metabolisme nukleotida dan laluan yang terlibat dalam penjanaan oksida dan antioksidan. Ini menunjukkan bahawa mereka terlibat dalam kemerosotan biofilm.

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Kajian ini telah menampilkan banyak data baru boleh menjelaskan biologi degradasi biofilm MRSA oleh faj. Hasil kajian ini dapat di gunakan bagi pembangunan terapi yang baru dan berkesan untuk mengatasi kesan biofilm MRSA.

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This thesis was submitted to the Senate of 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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LIST OF ABBREVIATIONS

ATP	Adenine triphosphate
bp	Basepair
$CaCl_2$	Calcium chloride
BLAST	Basic Local Alignment Search Tool
CFU	Colony forming units
CsCl	Cesium chloride
dsDNA	Double stranded DNA
EDTA	Ethylenediaminetetraacetic acid
ICTV	International committee on taxonomy of viruses
KCl	Potassium chloride
$MgSO_4$	Magnesium sulphate
µl	Microliter
ml	Milliliter
mM	Millimolar
MOI	Multiplicity of infection
NaCl	Sodium chloride
NCBI	National Center for Biotechnology Information
OD	Optical density
PEG	Polyethylene glycol
PFU	Plaque forming units
SM buffer	Salt magnesium buffer
TEM	Transmission electron microscope
TSA	Tryptone soya agar
CLSM	Confocal laser scanning microscopy
1D-SDS-PAGE	One-dimensional SDS-polyacrylamide gel electrophoresis
2D-SDS-PAGE	Two-dimensional SDS-polyacrylamide gel electrophoresis
2DE	Two-dimensional gel electrophoresis
SDS	Sodium dodecyl sulfate

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IPG	Immobilized pH gradient
CHAPS	3-[(3-Cholamidopropyl)dimethylammonio]-1-propanesulfonate
BSA	Bovine Serum Albumin
TCA	Trichloroacetic acid
DTT	Dithiothreitol
IAA	Iodoacetamide
CAN	Acetonitrile
TFA	Trifluoroacetic acid
MALDI- TOF MS	Matrix-Assisted Laser Desorption/Ionization- Time-Of-Flight Mass Spectrometer
PMF	Peptide Mass Fingerprinting
MALDI-TOF/TOF MS	Matrix-Assisted Laser Desorption/Ionization-Time-Of-Flight/ Time-Of-Flight Mass Spectrometer
CHCA	α-Cyano-4-hydroxycinnamic acid
NCBInr	National Center for Biotechnology Information nonredundant
UniProt	Universal protein knowledgebase
EXPASY	Expert Protein Analysis System
STRING	Search Tool for the Retrieval of Interacting Genes
KEGG	Kyoto Encyclopedia of Genes and Genomes
EC	Enzyme Commission number
PPI	Protein-Protein Interaction

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CHAPTER 1

INTRODUCTION

1.1 General background

Recent advances in medical therapeutics against methicillin-resistant *Staphylococcus aureus* (MRSA), are among the most important global effort towards curbing the spread of this pathogen currently affecting the human race. Therapeutic choices for MRSA infection treatments largely suffer from the development of resistance to antimicrobials by MRSA.

The ability of MRSA to form biofilm is a major contribution to bacterial virulence because the biofilm provides a well-structured and enclosed self-produced polymeric matrix that allows the bacterial cell to adhere to an inert or living surface (Franca *et al.*, 2012). Biofilm formation results from microbes reversibly attaching to a conditioned surface and releasing polysaccharides, proteins and extracellular DNA which allow the microorganisms to stick more stably to the surface (Willey *et al.*, 2008). Furthermore, the bacteria also have ability to develop another type biofilm by aggregating the bacteria in a cluster surrounded by an extracellular polymeric substance (EPS) matrix without attachment to the surface (Bjarnsholt *et al.*, 2013).

The EPS matrix in a biofilm provides a first line of protection to the bacterial cells from antibiotics and the penetrative attack of antibodies in the immune systems (De Beer *et al.*, 1997). This ultimately prevents phagocytes from being able to interact with the bacterial cells (Lam *et al.*, 1980). Nevertheless, bacterial tolerance to antibiotics within a biofilm is greatly enhanced compared to planktonic cells (Høiby *et al.*, 2010). In addition, the transfer of plasmids through conjugation results in the easy spread of these antibiotic resistance determinants (Hoyle & Costerton, 1991). Moreover, antibiotic resistance has been attributed to the decreased ability of the antimicrobial drugs to penetrate the EPS matrix, causing exposure of cells to sub-lethal antibiotic concentrations thus promoting resistance. There is also a decrease in metabolic activity of the inner cells within the biofilm due to reduced oxygen and nutrient concentrations (Høiby *et al.*, 2010) making antibiotics which are effective against the dividing bacteria ineffective. The lower metabolic activity of some cells can also be related to the presence of 'persister' cells. Although not resistant to antibiotics, these cells display tolerance to them and are not killed (Spoering & Lewis, 2001). This ability of multidrug tolerance (MDT) (while the causes are yet not very clear) is possibly due to a state where the bacteria are deeply dormant. As these dormant cells are not metabolizing they will not be affected by the antibiotics (Lewis, 2008). Instead of being eliminated, these dormant cells represent a possible source for repopulating the biofilms, making the antibiotic therapy useless (Moyed & Bertrand, 1983). In addition, the bacteria in biofilms are protected against other environmental stresses, such as UV light, acid exposure, metal toxicity dehydration as well as salinity (Espeland & Wetzel,

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2001; Magrex-Debar *et al.*, 2000; McNeill & Hamilton, 2003; Teitzel & Parsek, 2003). Biofilm association allows bacteria to colonize with fewer restrictions, persist and continue to establish infections and spread between hosts. It is thus imperative that there is a need to design and develop newer therapeutics towards mitigating these biofilmed bacterial infections.

Few therapeutic agents have been successfully developed for the prevention and disruption of biofilms (El-Azizi *et al.*, 2005). Bacteriophages (or phages, in short) have the potential to resolve the problem of MDR bacteria-producing biofilm. For more than five decades, phage bactericidal agents have been employed in the treatments of bacterial infections in human and other species (Abedon *et al.*, 2011). Nevertheless, studies assessing phage efficacy on biofilm eradication are still at its infancy stage although the potential of phage and phage lytic proteins for biofilm eradication is very promising (Fu *et al.*, 2010; Gutiérrez *et al.*, 2016). Moreover, the ubiquitous abundance of bacteriophages provides a broad spectrum of potential bacteria (Hendrix *et al.*, 1999) which can potentially be treated by phage therapy (Clokie *et al.*, 2011; Flores *et al.*, 2011; Ormala & Jalasvuori, 2013). Although the isolation of new phages against MRSA strains was found to be very difficult, some MRSA phages have been successfully isolated (Mattila *et al.*, 2015).

There is a complex network between phages and biofilm. These complexities are vital in providing a diverse inhibitory mechanism towards the host bacterial biofilm whilst facilitating phage-mediated lysis and extracellular DNA release. Mechanisms of host bacterial biofilm inhibition are diverse among some phage components, whereas some host biofilm formation are facilitated through phage-mediated lysis leading to extracellular DNA release. The latest studies highlight about contradictory mechanisms for some phage proteins that are known as phage moonlighting proteins or also known as phage-encoded dUTPases (Duts). It is possible that these proteins are responsible in allowing the bacteriophage to overcome the low or even no metabolism for bacteria within biofilm. These phage-encoded proteins have at least dual functions; the primary function within the phage and the other moonlight functions are related to biology of bacteria (Ranjan *et al.*, 2013).

However and according to Harper *et al.* (2014) phages are no doubt can be a strategic tool for biofilm removal: 1) their amplification allows penetration into the cell matrix in the biofilm; 2) they express complex EPS depolymerizing enzymes (an advantage regarding application of antimicrobial drugs); 3) phages can induce depolymerizing enzymes production from within the host genome; and 4) phage replication can prevent persistent cell proliferation. Thus, it is very advantageous to use these phages to eradicate and disperse biofilms whilst indirectly avoiding the side effects associated with the use of antimicrobial agents. Their production is inexpensive, simple and fast with no reported side effects as yet, and they are also environmentally friendly. They possess a very narrow host spectrum, are host specific without having any concomitant effect on the normal microflora, and they can self-replicate at site of infection with the presence of a host bacterium.

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1.2 Problem statement(s)

"The world is running out of antibiotics, WHO report confirms… (WHO, 2017)". The emerging antibiotic resistance levels in bacteria with biofilms are becoming an increasingly serious threat to global public health and costly for health care due to prolong hospitalization. Therefore, a potential alternative such as bacterial viruses (phages) which are the natural predators of bacteria and are as diverse as their hosts, should be explored. However, the information on the predatory antimicrobial mechanisms of these bacterial phages in the control of bacterial populations and degradation the biofilm are still lacking.

1.3 Objectives of the study

Understanding the potential mechanisms of phages in the reduction and dispersal of MRSA biofilms is the focus of this study based on the following objectives:

1. To assess the variation of MRSA biofilm content and their influence on bacterial adhesion and cohesion;
2. To isolate MRSA-specific phages from the environment and assess their lytic activity on MRSA planktonic growth, characterize them and evaluate their ability in the eradication MRSA biofilm based on *in vitro* static biofilm models;
3. To characterize the phages genetically and validate phages as virion-associated enzymes that degrade biofilm by zymogram assay; and
4. To study the phage-biofilm interaction based on proteomics.

There are seven different chapters in the thesis; Chapters 1and 2 introduce the research and presents the literature review; Chapter 3 investigates the specific background of MRSA biofilms that were used as substrates to isolate bacteriophage from environment; the isolation of new phages and their biological characterizations and their ability to disperse and reduce MRSA biofilms are evaluated as described in Chapter 4; the genome sequences of the phages and their ability to degrade biofilm based on zymogram assay are determined in Chapter 5 and the interaction between phage and biofilm are discussed in Chapter 6. The molecular basis regarding bacteriophage-host interaction, particularly the host stress response proteins and bacteriophages induced proteins are well documented. Proteomic approaches have become increasingly popular in phage-biofilm interaction studies. The proteomics studies for the interaction between phage and biofilm by two-dimensional polyacrylamide gel electrophoresis (2D-SDS-PAGE) and mass spectrometry (MS) are highly utilized to unravel the role of phage in biofilm degradation. The investigation of this interaction between phage and biofilm may answer many questions regarding ability of phage to degrade the biofilm and kill the bacteria. Lastly, the conclusions drawn from this study are presented in Chapter 7 with recommendations for further work.

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