UNIVERSITI PUTRA MALAYSIA

ISOLATION AND CHARACTERIZATION OF NOVEL PHAGES IN TREATING MULTIDRUG RESISTANT Klebsiella pneumoniae USING ZEBRAFISH LARVAE MODEL

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FBSB 2021 2

ISOLATION AND CHARACTERIZATION OF NOVEL PHAGES IN TREATING MULTIDRUG RESISTANT *Klebsiella pneumoniae* USING ZEBRAFISH LARVAE MODEL

By

OMAR ASSAFIRI

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

October 2020

DEDICATION

To

My family who has supported me along this long journey and gave me strength and joy that I need to complete 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

ISOLATION AND CHARACTERIZATION OF NOVEL PHAGES IN TREATING MULTIDRUG RESISTANT *Klebsiella pneumoniae* USING ZEBRAFISH LARVAE MODEL

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October 2020

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

As time progresses, *Klebsiella pneumoniae* is becoming more resistant to antibiotics, thus rendering them ineffective. Phages have the potential to replace the antibiotics. In this study, two phages, *Klebsiella* virus UPM2146 and φUPM1705, which were able to lyse *K. pneumoniae* ATCC BAA-2146 and ATCC BAA-1705, respectively were isolated from a polluted lake. These phages had a titer of 10^{12} PFU/ml and 10^{7} PFU/ml, respectively. Transmission electron micrographs showed that both phages belong to the order *Caudoviriales. Klebsiella* virus UPM2146 had an adsorption period of 2 min, a latent period of 20 min, a rise period of 5 min, and a burst size of 20 PFU/bacteria. φUPM1705 had an adsorption period of 2 min, a latent period of 75 min, a rise period of 45 min, and a burst size of 298 PFU/bacteria. Turbidity assay at multiplicities-of-infection (MOI) of 0.02, 0.2, and 2 indicated that *Klebsiella* virus UPM2146 and φUPM1705 were able to lyse their hosts at 60 min and 180 min, respectively. Furthermore, spot and efficiency-of-plating (EOP) tests indicated that *Klebsiella* virus UPM2146 had a narrow host-range lysing 22.72% of the *K. pneumoniae* species tested but φUPM1705 was only specific to its host. *Klebsiella* virus UPM2146 was selected for further analyses. Whole genomic sequencing revealed that *Klebsiella* virus UPM2146 has a double-stranded DNA genome of 160,795 bp with 214 putative open-reading-frames (ORF). *Klebsiella* virus UPM2146 is lytic, and lacking toxin and integrase genes. Phylogenetic tree analysis classified *Klebsiella* virus UPM2146 within the new *Ackermannviridae* family. The zebrafish larvae model was used to test the efficacy of *Klebsiella* virus UPM2146 in lysing *K. pneumoniae* ATCC BAA-2146. The larvae were able to survive up to 24 hours after 30 min exposure to the host bacteria. The appearance of a curved spine resembling a hook indicated dead larvae. Upon treatment with *Klebsiella* virus UPM2146, the zebrafish larvae was able

to survive up to 10 hours. Therefore, *Klebsiella* virus UPM2146 has the potential to be used in phage therapy.

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

PEMENCILAN DAN PENCIRIAN FAJ NOVEL DALAM MERAWAT *Klebsiella pneumoniae* YANG RINTANG TERHADAP PELBAGAI UBATAN DENGAN MENGGUNAKAN MODEL LARVA ZEBRAFISH

Oleh

OMAR ASSAFIRI

Oktober 2020

Pengerusi : Profesor Khatijah Mohamad Yusoff, PhD
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Seiring dengan masa, *Klebsiella pneumoniae* menjadi lebih rintang terhadap antibiotik, sehingga menjadikannya tidak berkesan. Faj berpotensi untuk menggantikan antibiotik. Dalam kajian ini, dua faj, *Klebsiella* virus UPM2146 dan φUPM1705, yang masing-masing dapat menjangkiti *K. pneumoniae* ATCC BAA-2146 dan ATCC BAA-1705, dipencilkan dari tasik yang tercemar. Faj tersebut masing-masing mempunyai titer 10^{12} PFU/ml dan 10^{7} PFU/ml. Mikrograf elektron pancaran menunjukkan bahawa kedua-dua faj tersebut tergolong dalam order *Caudoviriales*. *Klebsiella* virus UPM2146 mempunyai tempoh penjerapan 2 min, tempoh pendam 20 min, tempoh kenaikan 5 min, dan saiz pecah 20 PFU/bakteria. Asai kekeruhan pada "*multiplicity-of-infection*" (MOI) sebanyak 0.02, 0.2, dan 2.0 menunjukkan bahawa *Klebsiella* virus UPM2146 dan φUPM1705 masing-masing dapat membunuh perumah mereka pada 60 min dan 180 min. Tambahan pula, ujian titikan dan "*efficiency-of-plating*" (EOP) menunjukkan bahawa *Klebsiella* virus UPM2146 mempunyai julat perumah yang sempit sehingga dapat membunuh 22.72% spesies *K. pneumoniae* yang diuji tetapi φUPM1705 hanya khusus bagi perumahnya. *Klebsiella* virus UPM2146 dipilih untuk analisa lebih lanjut. Penjujukan keseluruhan genom menunjukkan bahawa *Klebsiella* virus UPM2146 mempunyai genom DNA bebenang dua 160,795 bp dengan 214 rangka bacaan terbuka (ORF). *Klebsiella* virus UPM2146 bersifat lisis, dan tidak mempunyai gen toksin dan integrase. Analisis filogenetik mengkelaskan *Klebsiella* virus UPM2146 dalam famili yang baru, *Ackermannviridae*. Model larva *zebrafish* digunakan untuk menguji keberkesanan *Klebsiella* virus UPM2146 dalam melisiskan *K. pneumoniae* ATCC BAA-2146. Larva tersebut dapat hidup sehingga 24 jam setelah dedahan selama 30 min kepada bakteria perumah. Penampilan tulang belakang yang melengkung dan menyerupai cangkuk menunjukkan larva

yang mati. Setelah dirawat dengan *Klebsiella* virus UPM2146, larva *zebrafish* dapat bertahan sehingga 10 jam. Oleh itu, *Klebsiella* virus UPM2146 berpotensi digunakan dalam terapi faj.

ACKNOWLEDGEMENTS

First and above all, I praise God, the almighty for providing me this opportunity, for protection, and granting me the capability to proceed successfully. This thesis appears in its current form due to the assistance and guidance of several people. I would therefore like to offer my sincere thanks to all of them.

I want to express my deep thanks to my supervisor Professor Dr. Khatijah Yusoff for her inspiration, kind support, warm encouragement, caring guidance, critical comments, and correction of the thesis. Her efforts, challenges and supervision brought this work towards a completion. May the Almighty God richly bless her. I am also very grateful to my co-supervisor Dr. Adelene Song Ai Lian, Dr. Irwan Hanish, and Associate Professor Dr. Tan Geok Hun for their help and support.

A special thanks to all the lecturers who during our weekly lab meeting helped in the discussions and gave constructive criticisms on my work. I also would like to express my gratitude to all my colleagues in both MBL Lab, Virology lab 1 and 2 at Biotech 2 and 3 for welcoming me so kindly during the time I stayed at the labs and for providing excellent laboratory environment.

I deeply thank and appreciate my family for their support, love, patience, and encouragements so this thesis is heartily dedicated to you.

I thank all who in one way or another contributed in the completion of this thesis.

Omar Assafiri

This thesis was submitted to the Senate of the Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Doctor of Philosophy. The members of the Supervisory Committee were as follows:

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CHAPTER 1

INTRODUCTION

1.1 Overview

Klebsiella pneumoniae is a Gram-negative bacterium belonging to *Klebsiella* genus of *Enterobacteriaceae* family. Over the last two decades, *K. pneumoniae* species are becoming more resistant to a wide spectrum of antibiotics such as augmentin and carbapenem (Ashurst & Dawson, 2020; Patilaya e*t al.*, 2019). The bacteria belong to the ESKAPE group of bacteria (*Enterococcus faecium, Staphylococcus aureus, K. pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa,* and the *Enterobacter* species) which is responsible for many nosocomial infections in hospitals (Pendleton *et al*., 2013). Moreover, continuous overuse of antibiotics in hospitals has led to the rise of multidrug-resistant (MDR) bacteria. Developing new antibiotics is becoming expensive and there seemed to be some difficulty in finding new classes of antibiotics. In addition, the number of people being infected and responsible for death worldwide by MDR is in continuous increase. For example, it has been reported that in New York City, about 30% of the patients in hospitals are carrying carbapenem resistant *Klebsiella* (Shlaes, 2010). According to the World Health Organization (WHO), 1.9 million deaths in the world are due to MDR bacterial infection (Chaudhary *et al*., 2014). Recently, it has been predicted that by the year 2050, MDR would be responsible for 10 million deaths per year (OECD, 2018). Thus, it is necessary to search for other alternatives to antibiotic treatment.

Phage therapy is the therapeutic use of lytic bacteriophages (or phages) to treat bacterial infections. Phages are highly selective in infecting and lysing their bacterial hosts (Haq *et al*., 2012). They can multiply their number exponentially after lysis of their host with low toxicity. They can release the capsule depolymerase enzyme such as lysozyme from the tail, which can break up the Gram-negative outer-membrane (Principi *et al*., 2019; Romero-Calle *et al*., 2019). They are considered to be useful for therapeutic purposes if they are stable at body temperature (37^{o}C) and pH of 7. The fast rate in clearing their host(s) *in vitro* is another important parameter (Weber-Dąbrowska *et al*., 2016). Strict lytic phages are considered to have great potential for phage therapy because of the absence of the genes like integrase gene which are involved in lysogeny (Monteiro *et al*., 2018).

Klebsiella phages have been isolated from different sources worldwide, most of which were from the order of *Caudovirales* (Herridge *et al.*, 2019). The main three branches within this order are *Myoviridae*, *Siphoviridae* and *Podoviridae*. In the review by Herridge *et al.* (2019), they mentioned that up 70 *K. pneumoniae* phages have been isolated and characterized. Nearly

50% of these phages were isolated from sewage. However, the number of these phages that have therapeutic potentials are limited due to the fact that it is required to have a phage cocktail to lyse multiple bacterial hosts since phages are highly specific (Principi *et al.*, 2019). On the other hand, broad range phages can lyse multiple species of bacteria, but it has the potential to lyse normal flora (Ilyina *et al.*, 2019); therefore, this indicates that phages which are more specific has better therapeutic potential. For instance, Vinodkumar *et al.* (2005) showed that their phage was able to protect mice which were infected with MDR *K. pneumoniae*. Many of such studies used *in vivo* mice models but as far as to our knowledge, there are no publications on phage therapy against *K. pneumoniae* using the zebrafish larvae model after a thorough literature search was done. The latter, however, has been studied for other pathogens such as *Vibrio anguillarum* (Silva *et al*., 2014) and *Enterococcus faecalis* (Al-zubidi *et al*., 2019).

1.2 Problem statement

Overuse of antibiotics has given rise to MDR bacteria such as MDR *Klebsiella pneumoniae* but very few new antibiotics are being discovered making it necessary to find an alternative in curing MDR *K. pneumoniae* infection.

1.3 Hypothesis

Lytic bacteriophages which are able to lyse and kill multiple antibiotic resistant *K. pneumoniae* may be used as alternative to antibiotics.

1.4 Objective of the study

This study aims to isolate phages from the environment, study their biological characteristics and their potential to be used in phage therapy against *K. pneumoniae*. Also, a specific phage was tested for therapeutic potential using zebrafish larvae model.

In order to achieve this, the specific objectives of this thesis were:

1. To isolate phages specific to MDR *K. pneumoniae* ATCC BAA-2146 and ATCC BAA-1705 from the environment, purify and characterize them;
2. To measure their *in vitro* plating efficiency against MDR *K. pneumoniae* ATCC BAA-2146 and ATCC BAA-1705;
3. To perform whole genomic sequencing on one selected phage genome and perform bioinformatics analysis; and
4. To investigate the capability of the selected phage in protecting zebrafish larvae against *K. pneumoniae* infection.

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