UNIVERSITI PUTRA MALAYSIA

GROWTH INHIBITORY POTENTIAL AND ANTI-METASTATIC EFFECT OF CAMEL URINE ON 4T1 CELL LINE In Vitro AND In Vivo

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By

MUHAMMAD FIRDAUS ROMLI

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

June 2016

DEDICATION

IN MEMORY OF
THE BRIGHTEST SISTER
I COULD EVER HAVE

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

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June 2016

Chairman : Nik Mohd Afizan Nik Abd Rahman, PhD
Faculty : Biotechnology and Biomolecular Sciences

Breast cancer has been a prominent health problem throughout the world, claiming thousands of lives directly or indirectly by metastasizing to distant organs of the body. Hence, researches have designed several drugs to combat breast cancer with acceptable efficacy displayed although it comes with terrible side effects and emergence of resistant strain after prolonged use of the drugs. Therefore, the public has pushed forward the need to discover new anti-cancer compound from natural extract which has similar properties as the drugs but with little or no side effect. Although it may sound disgusting, camel urine has been consumed extensively for years by the Middle Eastern as it is believed to be able to treat wide range of diseases such as fever, cold or even cancer, apparently. They usually take it by mixing small drops with camel milk or take it by itself directly. The project aims to study the effects of camel urine in inhibiting the growth potential and metastatic ability of 4T1 cancer cell line in vitro and in vivo. Based on the MTT result, the cytotoxicity of the camel urine against 4T1 cell was established and it was dose-dependent at 2 mg/mL. Additionally, the anti-metastatic potential of the camel urine was tested by running several assays such as scratch assay, migration and invasion assay and mouse aortic ring assay. Those assays displayed promising result in the ability of the camel urine to inhibit metastatic process of the 4T1 cells. In order to fully establish camel urine potential, an in vivo study was carried out by treating mice inoculated with 4T1 cells with two different doses of the camel urine at 120 mg/kg and 240 mg/kg. By the end of the treatment period, the tumor size in the low dose and high dose groups have reduced in size at 1.26 ± 0.07 g and 1.16 ± 0.27 g respectively as compared to the negative control group. Additional assays such as TUNEL assay, immunophenotyping, cytokine level detection assay, clonogenic assay and proteome profiler demonstrated the capability of the camel urine to reduce and inhibit the metastatic potential of 4T1 cells in vivo. High dose treatment inhibited the formation of colonies in the lung of the mice to 12 ± 1.53 while low dose treatment clocked in 26 ±

2.31 colonies. In conclusion, camel urine is justified to be consumed as a supplement to combat cancer as evidenced through the in vitro and in vivo studies carried out as it managed to reduce the tumor size and inhibit the metastatic events in the treated groups. Apart from that, this project has laid out the mechanisms employed by the substance to inhibit the growth and the metastatic process of 4T1 cell.

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

POTENSI PENGHALANGAN PEMBESARAN DAN KESAN ANTI-METASTASIS AIR KENCING UNTA KE ATAS SEL 4T1 *In Vitro* DAN *In Vivo*

Oleh

MUHAMMAD FIRDAUS ROMLI

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Pengerusi : Nik Mohd Afizan Nik Abd Rahman, PhD
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Barah payu dara merupakan satu masalah besar di seluruh dunia kerana ia mampu membunuh ribuan pesakit dengan bergerak ke organ lain di dalam badan. Oleh kerana itu, penyelidik telah mencipta beberapa ubat untuk melawan barah payu dara yang menunjukkan kesan yang memuaskan walaupun pengambilan ubat-ubatan tersebut untuk tempoh yang panjang boleh menyebabkan kesan sampingan yang serius. Maka, satu inisiatif telah dilancarkan untuk mencari ubat semulajadi yang mampu melawan kanser tetapi tidak mempunyai kesan sampingan. Penduduk Timur Tengah telah meminum air kencing unta kerana mereka percaya ia mampu untuk merawat pelbagai penyakit seperti demam dan selsema. Ia akan dicampur dengan susu unta sebelum diminum. Tujuan projek ini adalah untuk mengkaji kesan air kencing unta dalam menghalang potensi petumbuhan dan keupayaan metastasis sel 4T1 dalam in vitro dan in vivo. Berdasarkan keputusan MTT, air kencing unta mengakibatkan kesan toksik kepada sel 4T1 dan kesan ini terikat dengan dos yang digunakan. Tambahan pula, potensi air kencing unta dalam menyekat proses metastasis telah dikaji menggunakan beberapa eksperimen seperti penyembuhan luka, analisis migrasi/invasive dan pembentukan cincin aorta mencit. Eksperimen-eksperimen ini telah menunjukkan keputusan yang memberangsangkan dengan keberkesanan air kencing unta menyekat proses metastasis sel 4T1. Bagi memahami dengan lebih mendalam, satu kajian in vivo telah dijalankan dengan menyucuk sel 4T1 ke dalam mencit-mencit sebelum mereka dirawat dengan air kencing unta dalam dua dos yang berbeza iaitu 120 mg/kg dan 240 mg/kg. Apabila rawatan telah ditamatkan, ukuran ketumbuhan dalam mencit-mencit daripada kumpulan rawatan menurun kepada 1.26 ± 0.07 g dan 1.16 ± 0.27 g berbanding kumpulan kawalan. Eksperimen-eksperimen susulan seperti analisis TUNEL dan analisis clonogenic telah dijalankan dan memberi hasilan positif berkenaan kebolehan air kencing unta dalam menghalang potensi metastasis sel 4T1. Pembentukan koloni di dalam paru-paru mencit daripada kumpulan rawatan kepekatan tinggi

menurun kepada 12 ± 1.53 manakala pembentukan koloni dalam kumpulan rawatan kepekatan rendah adalah 26 ± 2.31 koloni. Sebagai kesimpulan, air kencing unta boleh diminum untuk membantu merawat kanser berdasarkan keputusan yang diperolehi daripada kajian-kajian in vitro dan in vivo. Kepekatan yang lebih tinggi memberi keputusan yang lebih baik. Tambahan pula, kajian ini telah merangka mekanisma yang digunakan oleh air kencing unta untuk menghalang pembesaran and proses metastasis sel 4T1.

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To name every single person who has helped me throughout this arduous journey is no simple task as each and every single small thing is a help to me and my human's memory is ever so limited. So, from the bottom of my humble heart, I thank everyone who has put forth time and energy, in ever so different way and capacity.

Still, to not acknowledge two beings who has been there for me through thick and thin is abominable; the Mother and Father. For believing in me failures after failures, no word of gratitude could ever surmount to it.
Thank you.

I certify that a Thesis Examination Committee has met on 15 June 2016 to conduct the final examination of Muhammad Firdaus Romli on his thesis entitled "Growth Inhibitory Potential and Anti-Metastatic Effect of Camel Urine on 4T1 Cell Line *In Vitro* and *In Vivo*" 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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This is to confirm that:

- the research conducted and the writing of this thesis was under our supervision;
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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS

ACTB	Beta Actin
CCL	Carbon tetrachloride
CFU	Colony forming unit
CTL	Cytotoxic T cells
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
ECM	Extracellular matrix
EDTA	Ethylediaminetetraacetic acid
ELISA	Enzyme-linked immunosorbent assay
ER	Estrogen receptor
FACS	Fluorescence-activated cell sorting
FBS	Fetal Bovine serum
FITC	Fluorescein isothiocyanate
GAPDH	Glyceraldehyde 3-phosphate dehydrogenase
G-CSF	Granulocyte-colony stimulating factor
GM-CSF	Granulocyte macrophage colony stimulating factor
MCP-1	Monocyte chemoattractant protein-1
H&E	Hematoxylin and eosin
HPRT	Hypoxanthine-guanine phosphoribosyltransferase
HRP	Horseradish peroxidase
IC50	Inhibitory Concentration 50
ICAM-1	Intercellular adhesion molecule
IL	Interleukin
IFN	Interferon
INOS	Inducible nitric oxide synthase
KOH	Potassium hydroxide
LDH	Lactate dehydrogenase
MDA	Malondialdehyde
MRNA	Messenger RNA
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
NAOH	Sodium hydroxide
NF-KB	Nuclear factor kappa-light-chain-enhancer of activated B cell
NK	Natural Killer
NO	Nitric oxide
PBS	Phosphate buffered saline
PCR	Polymerase chain reaction
QPCR	Quantitative PCR
RNA	Ribonucleic acid
RPMI	Roswell Park Memorial Institute
ROS	Reactive oxygen species
RT-PCR	Real time PCR
S.E.M	Standard error of means
Th	T helper
TUNEL	Terminal deoxynucleotidyl transferase dUTP nick end labeling

CHAPTER 1

INTRODUCTION

Cancer has been one of the major diseases plaguing the world for millennial where several thousands of new cases are reported each year with high fatality rate (B. Stewart & C. Wild, 2014). Women have a 1 in 8 chance of getting diagnosed with breast cancer while in Malaysia, it is the most common occurrence reported. Although conventional treatment such as chemotherapy is available to suppress the onset and progress of cancer, the severe side effects such as possibility of relapse and pain coupled with varied chance of success dampen the treatment (Group, 2005).

In order for a cancer treatment to be considered a viable option, it has to not only kill or slow down the growth of the tumor but it needs to stop the spread of the cancer as well. Metastasis is a process whereby cancer cell migrates to distant organ or secondary sites in the body and proliferate (Deryugina & Quigley, 2006). It is estimated that 90% of fatality in cancer patient are brought upon by metastasis instead of the primary tumor. For metastasis to take place, it needs to undergo several crucial steps such as angiogenesis and invasion where interference at any of the steps will lead to termination of the metastasis cascade (Leber & Efferth, 2009).

It is a common practice to use murine model, including murine cancer cell, when investigating the efficacy of a new substance. This is because it is easy to replicate and both in vitro and in vivo studies can be carried out using the same cell line. Apart from that, it is cheaper as well as the induction of human cancer cell in a murine model will require the use of nude mice which are expensive and require a special facility to house them which are not easily available (Le Magnen et al., 2016).

As gross as it sounds, the consumption of camel urine is one of the many treatment options available in the Arabian Peninsula for centuries. In recent years, its medicinal claim is put under scrutiny and the results are quite promising whereby it is reported to exhibit anti-fungal activity and able to protect liver from damage induced by CCL_4 (Al-Bashan, 2011; Alzahrani & Alharbi, 2011). Moreover, it is able to kill several cancer cell lines at an acceptable dosage (Al-Yousef et al., 2012; Alghamdi & Khorshid, 2012). Nonetheless, its mechanism in inhibiting the metastatic potential of cancer cell has not been properly investigated and there has been few animal models tested so far. It is hypothesized that camel urine will be able to inhibit the growth, migration and invasion of 4T1 cells in vitro. It will also be able to decrease the tumor size and reduce the expression of inflammation-related genes and angiogenesis-related proteins in vivo. As such, this study aimed to investigate the effect of camel urine on the growth and metastatic ability of 4T1 cells. The mechanism of camel urine inhibiting tumor growth and the metastasis process of breast cancer cell will be tested using several assays such as MTT assay, proteomic profiler assay and real-time PCR.

The objectives of this study were:

1. To assess the cytotoxic and anti-metastatic potential of camel urine against 4T1 cancer cell line in vitro.
2. To investigate the effect of camel urine in treating 4T1 cell-challenged Balb/c mice.
3. To determine the inflammation-related genes and angiogenesis-related proteins affected by camel urine in vivo.

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