UNIVERSITI PUTRA MALAYSIA

ANTIPROLIFERATIVE ACTIVITIES OF METHANOLIC EXTRACT OF Chromolaena odorata (L.) R.M. KING & H. ROB. IN A MICE MODEL

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By

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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

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Chairman : Associate Professor Arifah binti Abdul Kadir, PhD
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Chromolaena odorata and *Melastoma malabathricum* are plants that normally found in wasteland in Malaysia and both have great value in wound healing. Previous literatures reported that these plants possess antiproliferative, antibacterial and anti-inflammatory effects. This study was conducted to investigate the antiproliferative activity of the methanolic extract of *C.odorata* (MeCO) in a mice model. The antiproliferative effect was conducted by MTT assay and the results revealed that MeCO has higher antiproliferative effect with IC_{50} value 78 µg/ml compared with *M. malabathricum* (no IC_{50} value). Thus, MeCO was chosen for *in vivo* experiment. For acute oral toxicity study, mice were divided into two groups, control and treatment (5000 mg/kg of MeCO). Results showed that there was no significant different of mice administered with MeCO in body weight. However, food intake of treatment mice was significant different ($p < 0.05$) compared to control group. There was significant decrease ($p < 0.05$) of lung weight in treatment group compared to control group. However, there was no significant difference in relative organ weight of liver, kidney and spleen of the treatment group compared to control group. Besides, the serum biochemical analysis showed that there was no significant different of mice administered with plant extract compared to control except alkaline phosphatase (ALP). ALP was significantly lower ($p < 0.05$) compared to control group. Histological examination showed normal architecture for spleen and kidney in both groups. However, mild congestion observed in liver and lungs of treatment group. For efficacy study, the mice were divided into six groups ($n = 6$) which were 250 mg/kg MeCO, 500 mg/kg MeCO, 1000 mg/kg MeCO, control (normal), untreated control mice and vehicle control. The mean survival time of the treatment groups was significantly higher ($p < 0.05$) compared to untreated control group. The liver weight of untreated control, 250 mg/kg and 500 mg/kg was significantly higher ($p < 0.05$) compared normal group. Besides, the tumour weight of mice treated with 1000 mg/kg was significantly lower ($p < 0.05$) compared to untreated control group. Serum biochemical analysis showed that the glucose was significantly different ($p < 0.05$) in

all groups compared to the normal while urea level in vehicle control was significantly lower ($p < 0.05$) compared to normal. Histopathological examination resulted in metastasis of the mammary tumour to various organs such as spleen, liver, lungs in all groups. In conclusion, the MeCO extract has a potential of antiproliferative agent in breast cancer *in vitro* and *in vivo*.

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

AKTIVITI ANTIPROLIFERATIF EKSTRAK METANOL *Chromolaena odorata* (L.) R.M. KING & H. ROB. DI DALAM MODEL TIKUS

Oleh

NOR FAZIRAH BINTI ROSLI

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Chromolaena odorata dan *Melastoma malabathricum* adalah tumbuh-tumbuhan yang biasanya ditemui di tanah tandus di Malaysia dan kedua-duanya mempunyai nilai yang tinggi dalam penyembuhan luka. Kesusteraan terdahulu melaporkan bahawa tumbuhan ini mempunyai kesan antiproliferatif, antibakteria dan antiinflamasi. Kajian ini dijalankan untuk mengkaji aktiviti antiproliferatif ekstrak daun metanol *C. odorata* (MeCO) dalam model tikus. Kesan antiproliferatif dijalankan melalui ujian MTT dan hasilnya menunjukkan bahawa MeCO mempunyai kesan antiproliferatif yang lebih tinggi dengan nilai IC_{50} 78µg/ml berbanding dengan

M. malabathricum (tiada nilai IC_{50}). Oleh itu, MeCO dipilih untuk eksperimen *in vivo*.Untuk kajian ketoksikan akut secara oral, tikus-tikus dibahagikan kepada dua kumpulan, kawalan dan rawatan (5000 mg/kg MeCO). Keputusan menunjukkan bahawa tiada perbezaan yang signifikan antara tikus yang telah diberikan dengan MeCO dalam berat badan. Walaubagaimanapun, pengambilan makanan oleh kumpulan rawatan terdapat perbezaan yang signifikan ($p < 0.05$) berbanding dengan kumpulan kawalan. Terdapat penurunan berat yang signifikan ($p < 0.05$) pada paru-paru dalam kumpulan rawatan berbanding kumpulan kawalan. Namun, terdapat tiada perbezaan signifikan di dalam berat organ relatif hati, buah pinggang dan limpa dalam kumpulan rawatan berbanding kumpulan kawalan. Selain itu, analisis serum biokimia menunjukkan bahawa tiada perbezaan yang signifikan antara tikus yang diberikan dengan ekstrak tumbuhan berbanding dengan kawalan kecuali alkali fosfatase (ALP). ALP adalah penurunan yang signifikan ($p < 0.05$) berbanding kumpulan kawalan. Pemeriksaan histologi menunjukkan struktur normal untuk limpa dan buah pinggang dalam kedua-dua kumpulan. Walau bagaimanapun, kongesi dapat dilihat dalam hati dan paru-paru kumpulan rawatan.Untuk kajian keberkesanan, tikus-tikus dibahagikan kepada enam kumpulan ($n = 6$) iaitu 250 mg/kg MeCO, 500 mg/kg MeCO, 1000 mg/kg MeCO, kawalan (normal), tikus kawalan yang tidak dirawat dan kawalan

pembawa. Purata hayat oleh kumpulan rawatan peningkatan yang signifikan ($p < 0.05$) berbanding kumpulan yang tidak dirawat. Berat hati dalam kumpulan tidak dirawat, 250 mg/kg dan 500 mg/kg adalah peningkatan yang signifikan($p < 0.05$) berbanding kumpulan normal. Selain itu, berat tumor dalam tikus yang di rawat dengan 1000 mg/kg adalah penurunan yang signifikan ($p < 0.05$) Analisis serum biokimia menunjukkan bahawa glukos adalah perbezaan yang signifikan ($p < 0.05$) dalam semua kumpulan berbanding dengan normal manakala tahap urea dalam kumpulan pembawa adalah penurunan yang signifikan ($p < 0.05$) berbanding normal. Pemeriksaan histopatologi menunjukkan keputusan tumor mamma metastasis kepada pelbagai organ seperti limpa, hati, paru-paru dalam semua kumpulan. Sebagai kesimpulan, ekstrak MeCO mempunyai potensi agen antiproliferatif kanser payudara dalam in vitro dan in vivo.

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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 Master of Science. The members of the Supervisory Committee were as follows:

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LIST OF ABBREVIATIONS

µg/mL	microgram per mililiter
µl	microliter
Alb	Albumin
ALP	Alkaline phosphatase
ALT	Alanine transaminase
ANOVA	Analysis of variance
AS	Alveolar spaces
AST	Aspartate transaminase
ATCC	American Type Culture Collection
AWAB	Asian/West African biotype
BALB/c	Albino laboratory-bred strain of the house mouse
BC	Breast cancer
BL	Bronchial lumens
BSE	Breast self-examination
BV	Blood vessel
CA	Central arteriole
Cal51	Human breast adenocarcinoma cell line
Caov-3	Human ovarian adenocarcinoma cell line
CEM-SS	T-Lymphoblastic leukemia cell line
CGM	Complete Growth Medium
Chol	Cholesterol
CMF	Cyclophosphamide, Methotrexate and Fluorouracil
Creat	Creatinine
CT	Convoluted tubules

CV	Central vein
DMEM	Dulbecco's Modified Eagle Medium
DMSO	Dimethyl Sulfoxide
ER+	Oestrogen- positive
FBS	Foetal Bovine Serum
g/L	gram per liter
G	Glomerulus
GGT	Gamma-glutamyl transferase
GHS	Globally Harmonised Classification System
Gluc	Glucose
H and E	Hematoxylin and Eosin stain
HaCaT	Normal human keratinocyte cell line
HeLa	Human cervical adenocarcinoma cell line
HepG2	Hepatocellular carcinoma cancer cells
HL-60	Promyelocytic leukemia cell line
IACUC	Institutional Animal Care and Use Committee
IC_{50}	Half maximal inhibitory concentration
IL-1β	Interleukin 1 Beta
ILS	Increase in lifespan
LD_{50}	Median lethal dose
LDH	Lactate dehydrogenase
LLC	Lewis lung carcinoma cell line
LPS	Lipopolysaccharide
MARDI	Malaysian Agricultural Research and Development Institute
MCF	Human breast cancer cell line

MDA-MB-23	Human breast cancer cell line
mmol/L	milimol per liter
MST	Mean survival time
MTT assay	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium Bromide assay
NCI-H187	Human lung cancer cells
NF-$_{\kappa}$ B	Nuclear factor kappa-light-chain-enhancer of activated B cells
NO	Nitric Oxide
ºC	degree Celcius
OD	Optical Density
OECD	Organisation for Economic Cooperation and Development
PBS	Phosphate Buffer Solution
PR+	Progesterone- positive
PV	Portal vein
r/min	revolution per min
ROW	Relative organ weight
RP	Red pulp
rpm	rounds per minute
S	Sinusoids
SAB	Southern African biotype
SD	Standard deviation
SDS	Sodium Dodecyl Sulfate
T and CM	**T**raditional and **C**omplementary **M**edicine
Tbil	Total Bilirubin
TNFα	Tumour necrosis factor alpha

trypsin-EDTA	Trypsin - ethylenediaminetetraacetic acid
umol/L	micromol per liter
W	Final body weight
w/v	Weight per volume
W_0	Initial body weight
WP	White pulp

CHAPTER 1

INTRODUCTION

1.1 Background of study

Cancer is one of the leading causes of mortality in the world due to its complex nature. In medical term, cancer is known as malignant neoplasm, a disease that proliferates mammalian cells showing overgrowth behaviours, invasion of other nearby tissue by intrusion and destruction of surrounding matrix and metastasis to other organs through blood and lymph node vessels (Zhe, 2010). Among different types of cancer, one of the world burdens is breast cancer as 268 600 of invasive breast cancer cases are estimated to be diagnosed in the year 2019 (DeSantis *et al.*, 2019).

Numerous breast cancer treatments are available namely surgery, radiation, hormone therapy and immunotherapy. Nevertheless, not all treatments are suitable for the patients where some factors should be considered such as the tumour size, lymph nodes involvement and tumour stage (Bellavance and Kesmodel, 2016). Chemotherapy is a type of therapy using different types of drugs to treat cancer patients such as alkylating agents, antimetabolites, anti-microtubules and hormones. However, these clinical anticancer drugs give side effects depending on the types and doses of the drugs. Alkylating agents may cause secondary leukaemia (Zhang *et al.*, 2016). The antimetabolites contain several side effects which are immunosuppression, severe nausea and vomiting, ulcerative stomatitis and diarrhoea along with haemorrhagic enteritis. Whereas, anti-microtubules can cause neutropenia and peripheral neuropathy (Visconti and Grieco, 2017), and hormones therapy causes weight gain, oedema, vomiting, fatigue and sweating as well as constipation (Haidinger and Bauerfeind, 2019).

In regard with the side effects obtained during or following the treatment, the researches of plants as natural product for cancer treatment have increased due to the good impact on human wellness. Eighty percent of South-East Asian and African were reported using traditional and complementary medicine (TandCM) (WHO, 2019). Malaysian Agricultural Research and Development Institute (MARDI) recorded that herbal industry's market value had reached RM10 billion in 2008 and it will be projected to increase around RM32 billion in 2020 (Hafizudin *et al.*, 2015).

In ancient medicine, plant-derived chemicals were used to treat human diseases. In 1950s, researches of plant-derived anticancer started with the discovery of vinca alkaloids and podophyllotoxins (Juárez, 2014). Vinca alkaloids such as vinblastine and vincristine were isolated from *Cantharanthus roseus* or *Vinca rosea* which has been used for breast cancer treatment. One of the latest plant-derived anti breast cancer drugs is ellipticinium. It is a derivative of ellipticine and isolated from Apocynaceae family and it is now used as clinical drug called Elliptinium (Issa *et al.*, 2019). In line

with that, many researches have been conducted around the world to investigate new anticancer properties using plants.

Regarding the synthetic anticancer drugs which affect normal cells, the plants and their derived product usage as the treatment are among unresolved values controlling the malignancies (Mbaveng *et al.*, 2011). The discovery of a new alternative treatment using plant extracts is needed to treat breast cancer. In this study, two plants were used which are *C. odorata* and *M. malabathricum*.

C. odorata is a species of flowering shrub in sunflower family (Anyanwua *et al.*, 2017). Occasionally, it is grown as ornamental and medicinal plant. Due to hard growth control, it is a major weed to croplands and plantations (Chakraborty *et al.*, 2011). In Malaysia, it is called as 'pokok kapal terbang' (Jumaat *et al.*, 2017). In addition, it has a pungent and aromatic odour when crushed (Anyanwu *et al.*, 2018). Thais used *C. odorata* to treat skin diseases and insect bites (Pitakpawasutthi *et al.*, 2018).

Meanwhile, *M. malabathricum* is one of the species from Melastomaceae (Awang *et al.*, 2016). It can be found along the roadside in Malaysia. It is also classified as weed (Jaiosa *et al.*, 2016) and the whole part of this plant has been used as a medicine among the old folks (Khoo *et al.*, 2014). Rajenderan. (2010) reviewed that they used *M. malabathricum* as anti-haemorrhagic agents (leaves), besides treating stomach-ache (flowers) and measles (root). Hence, this study was conducted to investigate the antiproliferative activities of methanolic extract of *C.odorata* in a mouse 4T1 breast cancer model.

1.2 Objectives General objective:

To investigate the antiproliferative effect of methanolic *C. odorata* and *M. malabathricum* leaves extracts

The specific objectives of this study are:

1. To determine the cytotoxicity of methanolic *C. odorata* and *M. malabathricum* leaves extracts using MTT assay.
2. To investigate the acute toxicity study of *C. odorata* extract in female *BALB/c* mice.
3. To investigate the antiproliferative effects of methanolic extracts from *C. odorata* extract on mammary gland cancer in female *BALB/c* mice.

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LIST OF PUBLICATIONS

Proceeding

Nor Fazirah, R., Arifah, A. K. and Othman, F. (2015, November). *In vivo* investigation of antioxidant and antitumor activities of active fractions isolated from selected Malaysian plants. Paper presented at Post graduate colloquium No 8 at Faculty of Veterinary Medicine, Universiti Putra Malaysia, Serdang, Malaysia.

Nor Fazirah, R., Arifah, A.K. and Fauziah O. (2016, November). Investigation of antioxidant and anticancer activities of *Chromolaena odorata* and *Melastoma malabathricum* extracts. Paper presented at Postgraduate Colloquium No 8 at Faculty of Veterinary Medicine, Universiti Putra Malaysia, Serdang, Malaysia.

Nor Fazirah, R., Arifah, A. K. and Annas, S. (2018, July). Acute oral toxicity study of methanolic leaf extract of *Chromolaena odorata* in female *BALB/c* mice. Paper presented at 10th Malaysian Association of Veterinary Pathology (MAVP) Scientific Conference 2018 at Casuarina Meru Hotel, Ipoh, Malaysia.