UNIVERSITI PUTRA MALAYSIA

ENDOTHELIUM-DEPENDENT VASORELAXATION AND ANTIPROLIFERATION ACTIVITIES OF CHLOROFORM EXTRACT F5 FRACTION FROM Crinum amabile DONN EX KER GAWL. LEAVES

LIM CHUNG PIN

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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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May 2019

Chairman : Prof. Madya Rusliza Binti Basir, PhD
Faculty : Medicine and Health Sciences

Medicinal plants are potential sources of bioactive compounds, which due to their multiple pharmacological benefits, could be developed into promising therapeutic drugs. *Crinum amabile* possesses various biological activities such as antimalaria, anticancer and antihypertension. These encouraging findings had led to the selection of this plant species as a viable candidate for developments of anticancer and antihypertension products. Therefore, this research was undertaken to investigate the anticancer (cytotoxicity, apoptosis and anti-angiogenesis) and the antihypertensive properties of this plant. The possible pathways to the underlying mechanism of respective activities were also elucidated. Firstly, the leaves of *C. amabile* were serially extracted using Soxhlet's apparatus to yield four different extracts: petroleum ether extract (PE), chloroform extract (CE), methanol extract (ME) and water extract (WE). Preliminary assays (both anticancer and vasorelaxation) showed that CE exhibited the highest pharmacological effects. Thus, CE was fractionated using column chromatography and standardized through thin layer chromatography to produce six individual fractions. Next, the cytotoxicity of all these extracts and fractions were tested on various human cancer cell lines using MTS cytotoxicity assay. Results indicated that F5 fraction exhibited non-cell-specific cytostatic effects on most of the cancer cell lines, with MCF-7 breast cancer cells being the most susceptible. However, further studies using two apoptosis assays: annexin-V and DNA fragmentation assay showed that F5 fraction did not induce cell apoptosis on MCF-7 cells and no DNA fragmentations were detected. Nonetheless, cell proliferation assay using MTT assay revealed that F5 fraction was able to inhibit normal cell proliferation as well as VEGF-induced cell proliferation of normal endothelial cell: HUVECs. Data from this study illustrated that F5 fraction from leaf CE of *C. amabile* was able to exhibit cytostatic effect through anti-proliferation and anti-angiogenesis activities rather than induction of cell apoptosis. Meanwhile the vasorelaxation activities of *C. amabile* extracts and fractions were elucidated on both

phenylephrine pre-contracted intact and denuded rat aortic rings. The results indicated that F5 fraction exhibited the highest vasorelaxation activities and produced both endothelium-dependent and endothelium-independent vasorelaxation. In depth studies of its mechanism pathway(s) elucidated that the endothelium-dependent vasorelaxation induced by F5 fraction was primarily achieved through the stimulation of PGI_2 production and partial association with NO/sGC/cGMP activation pathway. The study proposed that *C. amabile* can serve as a promising lead candidate for both discovery and development of new cytotoxic or vasodilator drugs.

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

AKTIVITI VASORELAKSASI ENDOTELIUM BERGANTUNG DAN ANTI-PERCAMBAHAN EKSTRAK KLOROFORM PERCAHAN F5 DARIPADA DAUN *Crinum amabile* DONN EX KER GAWL.

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Tumbuhan perubatan merupakan sumber sebation bioaktif berpotensi yang boleh diperkembangkan menjadi ubat terapeutik yang menjanjikan disebabkan oleh pelbagai farmakologi faedahnya. *Crinum amabile* mempunyai pelbagai aktiviti biologi seperti anti-malaria, anti-kanser dan anti-hipertensi. Penemuan yang menggalakkan ini telah menyebabkan pemilihan spesis tumbuhan ini sebagai calon untuk perkembangan produk anti-kanser dan anti-hipertensi. Justeru itu, kajian ini telah dijalankan untuk menyiasat sifat anti-kanser (sitotoksik, apoptosis dan anti-angiogenesis) dan anti-hipertensi-nya. Laluan mekanisme untuk aktiviti masing-masing yang berkemungkinan juga diperjelaskan. Pertama-nya, daun *C. amabile* telah diekstrak dengan alatan soxhlet's untuk menghasilkan empat jenis ekstrak yang berbeza: ekstrak petroleum eter (PE), ekstrak kloroform (CE), ekstrak metanol (ME) dan ekstrak air (WE). Ujian permulaan (kedua-dua anti-kanser dan vasorelaksasi) menunjukkan bahawa CE menunjukkan kesan farmakologi yang tertinggi. Oleh itu, CE telah difraksinasikan dengan kromatografi lajur dan diseragamkan melalui kromatografi lapisan nipis untuk menghasilkan enam individu pecahan. Kemudian, kesan sitotoksik semua ekstrak dan pecahan telah diuji ke atas pelbagai sel kanser manusia melalui ujian sitotoksik MTS. Keputusan menunjukkan bahawa pecahan F5 memperlihatkan kesan sitostatik bukan sel khusus ke atas majoriti sel kanser, dengan sel kanser payudara MCF-7 merupakan sel yang paling mudah terpengaruh. Walau bagaimanapun, kajian lanjut menggunakan dua ujian apoptosis: annexin-V and ujian fragmentasi DNA menunjukkan bahawa pecahan F5 tidak mendorong apoptosis sel ke atas sel MCF-7 dan tiada fragmentasi DNA dikesan. Tambahan pula, penggujian percambahan sel dengan ujian MTT mendedahkan bahawa pecahan F5 dapat menghalang percambahan sel biasa serta percambahan sel yang didorong oleh VEGF dengan sel endotelial biasa: HUVEC. Data daripada kajian ini menggambarkan pecahan F5 dari CE daun *C. amabile* dapat memberikan kesan sitostatik melalui aktiviti anti-percambahan sel dan anti-angiogenesis, bukannya apoptosis sel.

Sementara itu, aktiviti vasorelaksasi ekstrak dan pecahan *C. amabile* telah dibuktikan ke atas phenylephrine pre-kontrak cincin aortik tikus. Hasil kajian menunjukkan bahawa pecahan F5 menunjukan aktiviti vasorelaksasi yang tertinggi yang merangkumi kedua-dua vasorelaksasi endotelium bergantung and endotelium tak bergantung. Kajian mendalam mengenai mekanisme laluannya menjelaskan bahawa vasorelaksasi endotelium bergantung yang didorong oleh pecahan F5 dicapai utamanya melalui stimulasi penghasilan PGI_2 dan sebahagian melalui laluan pengaktifan NO/sGC/cGMP. Kajian itu mencadangkan bahawa *C. amabile* boleh dijadikan sebagai calon yang menjanjikan untuk kedua-dua penemuan dan pembangunan ubat sitotoksik atau vasodilator yang baru.

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LIST OF ABBREVIATIONS

5-FU	5-Flourouracil
AA	Arachidonic Acid
AC	Adenylate Cyclase
ANOVA	Analysis of Variance
ATCC	American Type Culture Collection
ATP	Adenosine Triphosphate
BP	Blood Pressure
bp	Base Pair
BSC	Bio Safety Cabinet II
BSS	Blood Stasis Syndrome
C. amabile	*Crinum amabile*`
Ca^{2+}	Calcium ion
cAMP	Cyclic Adenosine 3',5'-Monophosphate
CC	Column Chromatography
CE	Chloroform Extract
cGMP	Cyclic 3',5'-Guanosine Monophosphate
COX	Cyclooxygenase
CVD	Cardiovascular Disease
DAG	Diacylglycerol
ddH_2O	Deionized Distilled Water
DMEM	Dulbecco's Modified Eagle's Medium
DMSO	Dimethyl Sulfoxide
EC_{50}	Concentration that produce 50% Activity

EDCF	Endothelium-Derived Contracting Factor
EDRF	Endothelium-Derived Relaxing Factor
EDTA	Ethylene Diamine Tetraacetate
ELISA	Enzyme-linked Immunosorbent Assay
ER	Estrogen Receptor
et al.	and Friends
EtBr	Ethidium Bromide
FBS	Fetal Bovine Serum
FGF	Fibroblast Growth Factor
FITC	Fluorescein Isothiocyanate
GDP	Guanosine Diphosphate
GPCR	Gqα-Protein-Coupled Receptor
GTP	Guanosine Triphosphate
HBD	Heparin-Binding Domain
HCT-116	Colon Carcinoma
HIV	Human Immunodeficiency Virus
HPLC	High Performance Liquid Chromatography
HPTLC	High Performance Thin Layer Chromatography
HT-29	Colon Adenocarcinoma
HUVEC	Human Umbilical Vein Endothelial Cell
IC_{50}	Concentration that inhibit 50% Activity
IP_3	Inositol Triphosphate
IP_3R	Inositol 1,4,5-triphosphate Receptor
K^+	Potassium ion
LDH	Lactate Dehydrogenase

L-NAME	L-NG Nitro-L-Arginine Methyl Ester
L-NNA	L-NG-Nitro Arginine
MB	Methylene Blue
MCF-7	Breast Carcinoma ER+
MDA-MB-231	Breast Carcinoma ER-
ME	Methanol Extract
Mg^{2+}	Magnesium ion
MLC	Myosin Light Chain
MLCK	Myosin Light Chain Kinase
MLCP	Myosin Light Chain Phosphatase
MMP	Matrix Metallo-Proteinase
MT-MMP	Membrane-Tethered Matrix Metallo-Proteinase
MTS	CellTiter 96® Aqueous Non-radioactive Cell Proliferation
MTT	3-(4,5-dimethylthiazolyl-2)-2, 5-diphenyltetrazolium Bromide
Na^{+}	Sodium ion
NCD	Non-Communicable Disease
NCI	National Cancer Institute
NO	Nitric Oxide
NOS	Nitric Oxide Synthase
NSAID	Non-steroidal Anti-inflammatory Drug
OD	Optical Density
P_x	Passage Number
PBS	Phosphate Buffered Saline
PCD	Programmed Cell Death
PE	Petroleum Ether Extract

PGI_2	Prostacyclin
pH	Exponent of Hydrogen ions
PI	Propidium Iodide
PIP_2	Phosphatidylinositol 4,5-Bisphosphate
PKA	Protein Kinase A
PKC	Protein Kinase C
PKG	Protein Kinase G
PLC	Phospholipase C
PMS	Phenazine Methosulfate
PS	Phosphatidylserine
psi	Pounds per Square Inch
R^2 value	Correlation Coefficient
Reh	Acute Lymphoma Leukemia
R_f value	Retention Factor
RhoGEF	Guanine Nucleotide Exchange Factor
Rmax	Maximum Percentage of Relaxation
ROCC	Receptor-operated Ca^{2+} Channel
rpm	Rotation per Minute
RPMI	Roswell Park Memorial Institute
RyR	Ryanodine Receptor
SD	Standard Deviation
SDS	Sodium Dodecyl Sulfate
SEM	Standard Error Mean
sGC	Soluble Guanylate Cyclase
SHR	Spontaneously Hypertensive Rat

SOCC	Store-operated Ca^{2+} Channel
SPSS	Statistical Package for Social Sciences
SR	Sarcoplasmic Reticulum
TAE	Tris-Acetate-EDTA
TE	Tris-EDTA
TK	Tyrosine Kinase
TLC	Thin Layer Chromatography
UPM	Universiti Putra Malaysia
UV	Ultra Violet
VEGF	Vascular Endothelial Growth Factor
VEGFR	Vascular Endothelial Growth Factor Receptor
VOCC	Voltage-operated Ca^{2+} Channel
VSMC	Vascular Smooth Muscle Cell
WE	Water Extract

CHAPTER 1

INTRODUCTION

Both cancer and hypertension have been identified as among the leading causes of death worldwide. Malaysia is no exception but actions taken to deal with the number of mortality and morbidity from these diseases has only seen modest progress (Ibrahim and Damasceno, 2012; Hail e*t al*., 2008). Therefore, there is an urge in seeking new and effective therapeutic drugs with minimal side effects (Wang *et al*., 2014). For thousands of years, humans have used plants and herbs as healing compounds to treat various illnesses (Goyal *et al.*, 2009). Medicinal plants have been proven to be a vital source of novel pharmacologically active compounds (Goyal *et al.*, 2009) which exhibit a variety of highly desirable therapeutic effects. Currently, there is growing awareness in several countries on the importance of native plant remedies in healthcare delivery system (Ch'ng *et al*., 2017). Many efforts have been concentrated on investigating the therapeutic efficacy of these local medicinal herbs since they are readily available (Taiwo *et al*., 2010). Development and transformation of these medicinal plants into highly valued commodities are essential to improve wellbeing on a global scale.

For centuries, *Crinum* spp. have been used to treat many diseases. Phytochemical analyses of these plants had yielded a vast array of compounds and most of them are identified as amaryllidaceae alkaloids. Since these alkaloids are shown to be highly bioactive, exhibited a wide range of pharmacological effects; many studies have been conducted to evaluate their therapeutic values (Oloyede *et al*., 2010; Thi Ngoc Tram *et al*., 2002). For examples, some literatures have shown that the alkaloids isolated from *Crinum amabile* bulbs possess promising cytotoxicity activities (Oloyede *et al*., 2010; Joshi *et al*., 2009; Viladomat *et al*., 1995; Likhitwitayawuid *et al.*, 1993), while others elucidated their vasorelaxation effects (Fennell and van Staden, 2001; Schmeda-Hirschmann *et al*., 2000). These promising findings have provided a rationale to explore the possibility of developing anticancer and antihypertension products from these alkaloids. However, while most of the papers focused on the bulb, no literature was found to describe the cytotoxicity and vasorelaxation activities of *C. amabile* leaves. Not to mention, no direct evidence was reported on the possible mechanistic pathway(s) underpinning the cytotoxicity and vasorelaxation activities.

Hence, the main objective of this research was aimed at elucidating the anticancer and vasorelaxation effects of *C. amabile.* To achieve the main objective, the following activities were carried out:

1. To fractionate the most active extract through biological activity guided fractionation.
2. To investigate the cytotoxicity activities of *C. amabile* leaves extracts and fractions.

3. To determine the mechanisms of action (apoptosis and anti-angiogenesis) of the cytotoxicity activity of the most active fraction of the most active *C. amabile* leaves extract.
4. To explore the vasorelaxation effects of *C. amabile* leaves extracts and fractions.
5. To elucidate the possible mechanistic pathway(s) involved in the vasorelaxation effect of the most active fraction of *C. amabile.*

With regards to the above, it is hypothesized that:

1. *C. amabile* leaves extracts and fractions produce cytotoxicity activities on various human cancer cell lines.
2. *C. amabile* leaves extracts and fractions are able to induce cell apoptosis, inhibit cell proliferation and suppress angiogenesis.
3. *C. amabile* leaves extracts and fractions exhibit vasorelaxation effects on rat aortic rings.
4. The possible mechanistic pathways involve in the vasorelaxation effect of *C. amabile* leaves extracts and fractions are associated with both endothelium-dependent and endothelium-independent vasorelaxation.

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