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EFFECTS OF CHEMICALLY SYNTHESIZED KAVA-KAVA (Piper methysticum G.Forst) FLAVOKAWAIN A AND B ON THE APOPTOTIC AND METASTATIC PROCESS OF MCF-7 AND MDA-MB231 CELLS IN VITRO AND 4T1 CELLS IN VIVO

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By

NADIAH ABU

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

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Chairperson: Assoc. Prof. Noorjahan Banu Alitheen, PhD
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In Malaysia, breast cancer is becoming a more prominent health issue among women today. Unfortunately, most malignant breast cancer will tend to metastasize to distant locations and form secondary tumors. This is usually the main cause of cancer-related deaths. Therefore, it is imperative to not actually treat cancer but to halt the metastatic process altogether. Though a number of approaches can be used to treat this disease, the prognosis tends to be unfavorable due to unwanted side effects and development of resistance. Natural products still remain one of the most sought after sources to find the perfect cure for cancer. The kava-kava (*Piper methysticum*) plant has been well known to aid illnesses and harness remedies since ancient times, especially in the pacific region. There are two classes of molecules that can be extracted from this kava-kava plant, kavalactones and chalcones. Chalcones can be divided into three types, flavokawain A, flavokawain B and flavokawain C. This project aims to study the effects of flavokawain A and B in the apoptotic and metastatic process in, MCF7 and MDA-MB231. Notably, both flavokawain A and B were non-toxic in both *in vitro* and *in vivo* experiments using Balb/C mice after 28 days of treatment. Through the MTT assay, it was found that both flavokawain A and B were cytotoxic in both breast cancer cell lines. Both flavokawain A and flavokawain B managed to induce apoptosis significantly as evidenced by these assays; double staining acridine orange/propidium iodide, flow cytometry cell cycle analysis, Annexin V analysis, JC-1, Caspase 8/9 fluorometric assay and BrdU cell proliferation assay. The results suggest that both flavokawain A and B induce G2/M arrest and apoptosis in both cell lines. Additionally, metastasis-related assays were also conducted such as; wound healing assay, migration and invasion assay, HUVEC tube formation and rat aortic ring assay. Flavokawain A and flavokawain B were shown to possess promising anti-metastatic potential. To further elucidate the apoptotic and anti-metastatic mechanism of flavokawain A and

B at the molecular level, real time polymerase chain reaction and western blot were conducted. Even though both molecules pose similar mechanism of action, flavokawain B is more potent and active than flavokawain A in terms of the induction of cell death and inhibition of metastasis. This notion was put to test in an *in vivo* setting whereby the compounds were used to treat 4T1 cells (mouse breast cancer) in mice. Based on the results, both flavokawain A and flavokawain B reduced the size of the tumor *in vivo*. In conclusion, flavokawain B is seemingly a better candidate as an anti-cancer agent than flavokawain A as evidenced by the *in vitro* assays. Moreover, based on the metastatic potential, flavokawain B was also a much more potent agent than flavokawain A. This concept was also proven by the *in vivo* assays using 4T1-breast cancer cell challenged mice. This study was able to elucidate the mechanism of action of both flavokawain A and flavokawain B in terms of its anti-cancer properties.

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

KESAN FLAVOKAWAIN A DAN FLAVOKAWAIN B KAVA-KAVA (*Piper methysticum* G.Forst) YANG DISINTESIS SECARA KIMIA TERHADAP PROSES ANTI-BARAH DAN ANTI-METASTATIK PADA MCF-7 DAN MDA-MB231 *IN VITRO* DAN SEL 4T1 *IN VIVO*

Oleh

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Insiden kes barah payu dara di kalangan wanita di Malaysia telah meningkat. Tambahan lagi, kes barah payu dara yang sudah mengalami metastasis juga meningkat. Barah payu dara yang telah metastasis akan membentuk kanser sekunder di tempat yang lain. Ini adalah penyebab utama kepada kematian yang disebabkan kanser. Oleh itu, adalah sangat penting untuk mengubati kanser dan menghalang proses metastasis. Walaupun terdapat banyak kaedah untuk mengubati kanser, kebanyakannya akan mengakibatkan kesan sampingan yang serius. Produk semulajadi telah menyediakan platform yang luas untuk mencari agen anti-barah yang efektif. Pokok kava-kava telah lama digunakan oleh orang kepulauan pasifik untuk merawat pelbagai penyakit. Terdapat dua kelas molekul yang boleh diekstrak dari pokok kava-kava; kavalactones dan chalcones. Kumpulan molekul chalcone boleh dibahagikan kepada tiga jenis; flavokawain A, flavokawain B dan flavokawain C. Aktiviti biologikal flavokawain A dan flavokawain B telah dilaporkan di dalam jurnal berwasit. Objektif kajian ini adalah untuk menilai kesan flavokawain A dan flavokawain B terhadap proses apoptosis dan metastasis di dalam dua jenis sel barah payu dara; MCF-7 dan MDA-MB231. Kedua-dua flavokawain A dan B tidak toksik kepada sel-sel normal di dalam kajian *in vitro* dan *in vivo* terhadap mencit Balb/C. Di samping itu, melalui eksperimen MTT, kedua-dua flavokawain A dan B mengakibatkan kesan toksik hanya kepada sel MCF-7 dan MDA-MB231. Untuk lebih memahami kesan flavokawain A dan flavokawain B, beberapa eksperimen lain dijalankan seperti, pewarnaan AO/PI, BrdU, analisis annexin V, analisis kitaran sel, analisis JC-1, analisis caspase 8/9, real-time PCR dan western blot. Tambahan pula, eksperimen untuk menentukan kesan anti-metastasis juga dijalankan seperti, penyembuhan luka, analisis migrasi/invasif *in vitro* , pembentukan cincin aorta tikus pembentukan tiub di dalam HUVEC sel, real time PCR dan western blot.

Berdasarkan keputusan yang diperoleh, flavokawain A dan flavokawain B mengakibatkan penahanan di fasa G2/M di dalam kitaran sel dan juga mencetuskan apoptosis. Selain itu, kedua-dua flavokawain A dan B juga mampu menghalang proses metastasis *in vitro* dengan signifikannya. Di antara flavokawain A dan flavokawain B, berdasarkan keputusan eksperiment, flavokawain B bertindak dengan lebih baik dalam membunuh kanser sel dan menghalang metastasis. Di dalam keadaan *in vivo,* flavokawain B juga bertindak dengan lebih efektif berbanding flavokawain A. Kesimpulannya, flavokawain B merupakan calon agen anti-kanser yang baik kerana ia mampu mencetuskan apoptosis di dalam kanser sel dan mampu menghentikan proses metastasis *in vitro* dan *in vivo.*

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I certify that a Thesis Examination Committee has met on (date of viva voce) to conduct the final examination of Nadiah Abu on her thesis entitled EFFECTS OF CHEMICALLY SYNTHESIZED KAVA-KAVA (*Piper methysticum*) FLAVOKAWAIN A AND B ON THE APOPTOTIC AND METASTATIC PROCESS ON TWO BREAST CANCER CELL LINES, MCF-7 AND MDA-MB231 CELLS *IN VITRO* AND 4T1 CELLS *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 Doctor of Philosophy

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This thesis was submitted to the Senate of 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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LIST OF ABBREVIATIONS

ACTB	Beta Actin
ALP	Alkaline Phosphatase
ALT	Alanine aminotransferase
AO	Acridine Orange
APC	Antigen Presenting Cell
AST	Aspartate aminotransferase
ATCC	American Tissue Culture Collection
ATP	Adenosine Triphosphate
BAX	BCL-2-Associated X Protein
BCL-2	B-Cell Lymphoma 2
BrdU	Bromodeoxyuridine
BSA	Bovine serum albumin
cDNA	Complementary DNA
COX-2	Cyclooxygenase 2
Ct	Threshold cycle
CTL	Cytotoxic T cells
CXCR4	C-X-C Chemokine receptor type 4
DAB	Diaminobenzidine
DMEM	Dulbecco's Modified Eagle Medium
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid

ECM	Extracellular matrix
EDTA	Ethylenediaminetetraacetic acid
ELISA	Enzyme-linked immunosorbent assay
ER	Estrogen Receptor
FACS	Fluorescence-activated cell sorting
FBS	Fetal Bovine Serum
FITC	Fluorescein isothiocyanate
FKA	Flavokawain A
FKB	Flavokawain B
FOXM	Forkhead box protein M1
GAPDH	Glyceraldehyde 3-phosphate dehydrogenase
GLUT	Glucose Transporter
H&E	Hematoxylin and eosin
HEGF	Human endothelial growth factor
HPRT	Hypoxanthine-guanine phosphoribosyltransferase
HRP	Horseradish peroxidase
HSP	Heat shock protein
IC50	Inhibitory Concentration 50
ICAM-1	Intercellular Adhesion Molecule
IL	Interleukin
IFN	Interferon
INOS	Inducible nitric oxide synthase
JC-1	5,5',6,6'-tetrachloro-1,1',3,3'

	tetraethylbenzimidazolylcarbocyanine iodide
JNK	c-Jun N-terminal kinases
KOH	Potassium hydroxide
LDH	Lactate dehydrogenase
MG/KG BW	Mg/kg body weight
MHC	Major histocompatibility complex
MMP9	Matrix metalloproteinase 9
MRNA	Messenger RNA
MRP-1	Multidrug resistance protein 1
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 cells)
NK	Natural Killer
NMR	Nuclear magnetic resonance
NO	Nitric oxide
P-AKT	Phosphor AKT
PBS	Phosphate buffered saline
PCR	Polymerase chain reaction
PE	Phycoerythrin
PI	Propidium iodide
PLK	Polo-like kinase
PS	phosphatidylserine

QPCR	Quantitative PCR
RNA	Ribonucleic acid
RPMI	Roswell Park Memorial Institute
ROS	Reactive oxygen species
RT-PCR	Reverse transcriptase PCR
S.E.M	Standard error of means
SDS-PAGE	Sodium dodecyl sulfate polyacrylamide gel electrophoresis
TdT	Terminal deoxynucleotidyl transferase
Th	T helper
TMB	3,3',5,5'-Tetramethylbenzidine
TUNEL	Terminal deoxynucleotidyl transferase dUTP nick end labeling
VEGF	Vascular endothelial growth factor

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CHAPTER 1

INTRODUCTION

Cancer has become a global burden as the number of new cases increases year by year (Siegel *et al.*, 2013). In women today, breast cancer has been one of the leading causes of cancer-related fatalities. This unfortunate incident has been linked to various factors including lack of a viable treatment, late screening for cancer patients and the lack of awareness among women to self-screen. In Malaysia, the number of new cases of breast cancer patients has also been increasing annually (Hisham *et al.*, 2004; Yip *et al.*, 2006). It is estimated that in 1 out of 16 women will be diagnosed with breast cancer at some point in their lives (Siegel *et al.*, 2013). Although conventional treatments including chemotherapy and surgery are widely used, these methods have several drawbacks including physical pain, increased relapse and lower survival rate (Bauma *et al.*, 2005; Ganz *et al.*, 2011).

One of the main reasons of administering anti-cancer agents in cancer patients is to eliminate cancer cells; it is also favorable that it inhibits the metastatic process as well (Zijl *et al.*, 2011). Metastasis is a process whereby primary tumor cells migrate and invade to form secondary tumors at a distant site, or secondary location (Zijl *et al.*, 2011). Metastasis accounts for more than 90% of cancer-related fatalities (Finger *et al.*, 2010; Lu *et al.*, 2009). There are several steps in the metastasis cascade including extravasation, migration, tissue invasion, angiogenesis and circulation (Fidler, 2000; Finger *et al.*, 2010). The most common sites of breast cancer metastasis is the lung, bone and liver (Weigelt *et al.*, 2005).

Natural products have played an important part in search for new drugs, even some of the most famous widely used drugs are derived from natural sources (Newman *et al.*, 2012; Rocha *et al.*, 2001). Kava-kava (*Piper methysticum*) plant is an evergreen shrub that is widely consumed in the pacific region (Dharmaratne *et al.*, 2002; Lebot *et al.*, 1997). Moreover, this plant is largely known to be involved in a wide spectrum of biological activities including, anti-inflammation, anti-bacterial and most importantly, anti-cancer (Tang *et al.*, 2008). Intriguingly, there has been a correlation between the consumption of kava-kava and the incidence of cancer (Steiner, 2000).

There are several interesting components that can be found in the kava root extracts, including chalcones (Dharmaratne *et al.*, 2002; Tang *et al.*, 2008). Chalcones are open ring flavonoids that are widely synthesized in the plant kingdom (Batovska *et al.*, 2010). Flavokawain A is a chalcone and has been reported to possess promising anti-cancer and anti-inflammatory activities (Tang *et al.*, 2008). Additionally, flavokawain A was found to inhibit the growth of bladder cancer cell lines *in vitro* (Tang *et al.*, 2008). Based on

the preliminary study, flavokawain A was found to have similar potential cytotoxic activities in breast cancer as in bladder cancer cells. Flavokawain B on the other hand, is a much better studied chalcone as compared to flavokawain A. It has been put forward that flavokawain B possess promising anti-inflammatory and antinociceptive properties (Kuo*et al.*, 2010; Kwon *et al.*, 2013). The promising anti-cancer properties of flavokawain B have also been tested in oral carcinoma, synovial sarcoma and liver cancer (Kuo *et al.*, 2010; Sakai *et al.*, 2011; Tang *et al.*, 2010). Nevertheless, though as hopeful as flavokawain A and flavokawain B may seem, further in depth mechanism as well as the anti-metastatic values is still yet to be discovered, especially in breast cancer. Moreover, the safety profile of the flavokawain A and B should also be tested even though the anti-cancer activities are promising. To achieve the objectives of this study several bioassays were attempted such MTT analysis, flow cytometry analysis, real-time PCR and western blot.

The objectives of this study were:

1. To assess and compare the *in vitro* toxicity and *in vivo* immunomodulatory potential of both flavokawain A and flavokawain B.
2. To investigate the cytotoxic effects and anti-metastatic potential of flavokawain A in two breast cancer cell lines, MCF-7 and MDA-MB231 *in vitro.*
3. To assess the anti-cancer mechanism of flavokawain B in terms of induction of cell death and anti-metastatic abilities in MCF-7 and MDA-MB231 *in vitro*.
4. To evaluate the anti-cancer activity of flavokawain A in an *in vivo* setting; 4T1-breast cancer challenged mice.
5. To determine the anti-cancer activity of flavokawain B in 4T1-breast cancer challenged mice *in vivo*.

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