UNIVERSITI PUTRA MALAYSIA

IMMUNOMODULATORY ACTIVITY OF Moringa oleifera L. LEAF ETHANOL EXTRACT ON NORMAL LYMPHOCYTES AND LEUKAEMIC CELL LINES

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By

HAMZA LAWAL

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

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DEDICATIONS

This is for you, Mama.

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirements for the degree of Master of Science

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April 2018

Chairman : Associate Professor Rajesh Ramasamy, PhD
Faculty : Medicine and Health Sciences

Moringa oleifera (M. oleifera), a member of the family Moringaceae, is a small-medium sized tree, 10-15m high, widely cultivated in East and Southeast Asia, West Indies and Polynesia. Indians have been using leaves, fruits and flowers of *M. oleifera* as part of their routine diet as this 'wonder' herb also was used in ancient Ayurveda and Siddha medicine for nearly 2000 years. Phytochemical and animal studies have shown that the therapeutic activities of *M. oleifera* have largely depended on its main polyphenols such as quercetin glucosides, kaempferol glycosides, rutin, and chlorogenic acid. To date, *M. oleifera* has been studied for their anti-oxidative, antidiabetic, anti-inflammatory and anticancer activity, yet their role in modulating the immune system is still elusive. The present study, therefore, aimed to investigate the in vitro immunomodulatory effect of *M. oleifera* leaves' ethanol extracts (MOETE) on healthy peripheral blood mononuclear cells (PBMCs) and leukaemic cell lines. Fresh and healthy leaves of *M. oleifera* were collected from an herbal farm located at Kampar, Selangor. Extracts of *M. oleifera* leaves were obtained using the mixture of ethanol and water at ratios of 100:0 (100% ethanol), 70:30 (70% ethanol), 50:50 (50% ethanol) and 0:100 (aqueous) as extraction solvents. Healthy donors were used as a source of primary lymphocytes while Jurkat and BV173 cells were utilised as transformed cell lines of T cells and B cells, respectively. The cytotoxicity of aqueous and ethanolic extracts of *M. oleifera* leaves on the cells was determined using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay while the marker compounds (quercetin, and kaempferol 3-O-glucoside) in *M. oleifera* extract were identified and quantified using High Performance Liquid Chromatography (HPLC). The immunomodulatory effect was evaluated through cell proliferation assays, cell cycle analysis and apoptosis assays. The antitumour potential of the extract on Jurkat and BV173 cells was further explored via global secretome and apoptotic proteins proteome arrays.

From the cytotoxicity analysis, 70% ethanol *M. oleifera* leaves extract exerted a dose-dependent stimulatory effect on PBMCs with an EC_{50} of 28±3 g/mL as well as cytotoxic effects on BV173 (IC_{50} = 125±6 g/mL) and Jurkat cells (IC_{50} = 262±3 g/mL). Also, from the HPLC analysis, kaempferol 3-O-glucoside (standard Rt = 32.689 vs sample mean Rt = 32.671), and quercetin (standard Rt = 42.020 vs sample mean Rt = 41.981) were identified. The extract enhanced the viability and proliferation of PBMCs by committing the cells into the cell cycle and reducing apoptosis while exerting anti-proliferative effects, cell cycle arrest and apoptosis in tumour cell lines. Also, the extract induced overexpression of pro-apoptotic cytokines and proteins but suppressed the expression of angiogenic factors and pro-survival proteins in tumour cell lines. Pathway enrichment analysis revealed that MOETE induced apoptosis in BV173 and Jurkat cells mainly through activation of the mitochondrial apoptotic pathway by upregulation of mitochondrial pro-apoptotic B cell lymphoma 2 (BCL2) family of proteins like the BCL-2-associated X protein (BAX) and the BCL-2 homologous antagonist killer (BAK) while downregulation of the anti-apoptotic protein, BCL-2. *M. oleifera* ethanol extract has immunostimulatory properties on normal lymphocytes and antitumour activity on leukemic cell lines. These abilities can be exploited in developing herbal supplements that strengthen the immune system to support aged and immunocompromised individuals as well as serve as adjuvants in therapies against blood cancers.

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

AKTIVITI IMMUNOMODULATORY DAUN KACANG KELOR YANG DIETANOL-EKSTRAK TERHADAP LIMFOSIT NORMAL DAN SEL-SEL KANSER LEUKEMIA

Oleh

HAMZA LAWAL

April 2018

Pengerusi : Profesor Madya Rajesh Ramasamy, PhD
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Moringa oleifera (M. oleifera), dari keluarga Moringaceae, adalah pokok bersaiz sederhana kecil, berketinggian 10-15m yang ditanam secara meluas di Timur dan Asia Tenggara, Hindia Barat serta Polynesia. Di Malaysia, kaum India telah menggunakan daun, buah-buahan dan bunga *M. oleifera* sebagai sebahagian daripada makanan rutin memandangkan ianya juga digunakan dalam perubatan Ayurveda dan Siddha selama hampir 2000 tahun. Kajian fitokimia dan haiwan telah menunjukkan bahawa aktiviti terapi M. oleifera sebahagian besarnya bergantung kepada polifenol utama seperti quercetin glukosida, kaempferol glukosida, rutin, dan asid klorogenik. Sehingga kini, *M. oleifera* telah dikaji kerana aktiviti anti-oksidatif, anti-diabetik, anti-radang dan anti-kansernya. Walaubagaimanapun, peranannya dalam modulasi sistem imun masih sukar untuk difahami. Oleh itu, kajian ini dijalankan bertujuan untuk mengkaji kesan imunomodulator ekstrak etanol daun *M. oleifera* (MOETE) pada sel mononuklear darah periferal (PBMCs) dan sel leukaemik secara *in vitro*. Daun *M. oleifer*a dikumpulkan dari ladang herba yang terletak di Kampar, Selangor. Ekstrak daun *M. oleifera* diperoleh menggunakan campuran etanol dan air pada nisbah 100: 0 (100% etanol), 70:30 (70% etanol), 50:50 (50% etanol) dan 0:100 (air) sebagai pelarut ekstraksi. Penderma sihat digunakan sebagai sumber sel darah putih utama manakala sel Jurkat dan BV173 digunakan sebagai sel-sel transformasi T dan B. Sitotoksisiti ekstrak air dan etanol daun *M. oleifera* pada sel telah ditentukan dengan menggunakan ujian 3- (4,5-dimetilthiazol-2-yl) -2,5-diphenyltetrazolium bromida (MTT) manakala sebatian penanda (quercetin, dan kaempferol 3-O-glukosida) dalam ekstrak *M. oleifera* telah dikenalpasti dan dikira menggunakan Kromatografi Liquid Performance High (HPLC). Kesan imunomodulator telah dinilai melalui ujian proliferasi sel, analisis kitaran sel dan pemeriksaan apoptosis. Potensi anti-tumor ekstrak pada sel-sel Jurkat dan BV173 terus diterokai menerusi ‘global secretome’ dan apoptosis protein ‘proteome arrays’.

Dari analisis sitotoksisiti, ekstrak 70% etanol daun *M. oleifera* memberikan kesan stimulasi yang kebergantungan-dos pada PBMC dengan EC_{50} kadar 28 ± 3 g/mL serta kesan sitotoksik pada BV173 (IC_{50} = 125 ± 6 g / mL) dan sel Jurkat (IC_{50} = 262 ± 3 g/mL). Selain itu, dari analisa HPLC, kaempferol 3-O-glukosida (standard Rt = 32.689 berbanding purata sampel Rt = 32.671), dan quercetin (standard Rt = 42.020 berbanding purata sampel Rt = 41.981) telah dikenalpasti. Ekstrak itu meningkatkan viabiliti dan proliferasi PBMC melalui modulasi kitaran hidup sel dan mengurangkan kadar apoptosis, sambil memberi kesan-kesan anti-proliferatif, perhentian kitaran sel dan apoptosis dalam sel-sel tumor. Juga, ekstrak dapat menjana tingi expressi sitokin dan protein pro-apoptosis sementara dapat menyekat expresi factor-faktor angiogenik dan 'pro-survival' protein dalam sel-sel sel tumor. Analisa 'pathway enrichment' mendedahkan bahawa MOETE dapat menyebabkan apoptosis dalam sel BV173 dan sel Jurkat terutamanya melalui pengaktifan laluan apoptosis mitokondria dengan menaik-expresi protein pro-apoptosis B lymphoma 2 (BCL2) mitokondria seperti protein X BCL-2 yang berkaitan (BAX), dan pe-nyah antagonis homologous BCL-2 (BAK) sementara mengurangkan protein anti-apoptosis, BCL-2. Ekstrak etanol *M. oleifera* mempunyai sifat immunostimulatori pada limfosit normal namun aktiviti anti-tumor pada sel-sel leukemia. Keupayaan ini dapat dieksploitasi dalam mengembangkan industry suplemen herba bagi menguatkan sistem kekebalan tubuh bagi individu yang berumur dan juga imunokompromi serta berperanan sebagai pembantu dalam terapi terhadap kanser darah.

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I certify that a Thesis Examination Committee has met on 17 April 2018 to conduct the final examination of Hamza Lawal on his thesis entitled "Immunomodulatory Activity of *Moringa oleifera* L. Leaf Ethanol Extract on Normal Lymphocytes and Leukaemic Cell Lines" 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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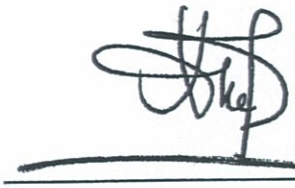

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This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Master of Science. The members of the Supervisory Committee were as follows:

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Name of Member of Supervisory Committee: Associate Professor Dr. Subashini C. Thambiah

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Ang	Angiogenin
Apaf-1	Apoptotic protease activating factor 1
APCs	Antigen-presenting cells
ATCC	American type culture collection
BAD	Bcl-2-associated death promoter
BAX	Bcl-2-associated X protein
Bcl-2	B cell lymphoma 2
BCLx	B-cell lymphoma X
BCR	B- cell receptor
BID	Bax-like BH3 protein
c-FLIP	Cellular (FADD-like IL-1β-converting enzyme [FLICE])-inhibitory protein
CAD	Caspase-activated Dnases
Casp	Caspase
CD	Cluster of differentiation
CDK	Cyclin-dependent kinase
CHI3L	Chitinase-3-like protein
CMI	Cell-mediated immunity
Con A	Concanavalin A
Cripto	Cryptic family protein
Cyt-c	Cytochrome c
DECs	Differentially expressed cytokines
DEPs	Differentially expressed proteins
DIABLO	Direct IAP-Binding protein with Low PI
DISC	Death inducing signaling complex
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
DR	Death receptor
EC50	Half maximal effective concentration
FAS	First apoptotic signal
FACS	Fluorescence-activated cell sorting
FADD	Fas associated death domain
FGF	Fibroblast growth factors
FITC	Fluorescein isothiocyanate
G	Gap
GM-CSF	Granulocyte–macrophage colony-stimulating factor
GO	Gene ontology

HAVCR	Hepatitis A virus cellular receptor
HO	Heme oxygenase
HMRC	Herbal Medicine Research Centre
HPLC-DAD	High-Performance Liquid Chromatography with Diode-Array Detection
HRP	Horse radish peroxidase
HSP	Heat shock protein
IAP	Inhibitor of apoptosis protein
IC50	Half maximal inhibitory concentration
IFN	Interferon
IGFBP	Insulin-like growth factor-binding protein
IL	Interleukin
IMR	Institute for Medical Research
IUPAC	International Union of Pure and Applied Chemistry
KEGG	Kyoto encyclopaedia of genes and genomes
JAK	Janus kinase
LC-MS	Liquid chromatography mass spectrometry
LPS	Lipopolysaccharide
LT	Lymphotoxin
M	Mitosis
MHC	Major histocompatibility complex
MOETE	M. oleifera leaves ethanol extract
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
NCBI	National Center for Biotechnology Information
NF-kB	Nuclear factor – kappa beta
NK	Natural killer
PBMCs	Peripheral blood mononuclear cells
PBS	Phosphate-buffered Saline
PHA	Phytohemagglutinin
PI	Propidium iodide
PI3K	Phosphoinositide 3-kinase
PS	Phosphatidylserine
PWM	Pokeweed mitogen
Rb	Retinoblastoma
RNA	Ribonucleic acid
RNase	Ribonuclease
ROS	Reactive oxygen species
RPMI	Roswell park memorial institute
S	Synthesis
SD	Standard deviation
SMAC	Second Mitochondria-derived Activator of Caspases

STAT	Signal transducer and activator of transcription
TAAs	Tumour associated antigens
TCR	T-cell receptor
TGF	Transforming growth factor
TGF	Transforming growth factor
Th	T-helper
TNF	Tumour necrosis factor
TNFSF	TNF superfamily
TRAIL R	TNF-related apoptosis-inducing ligand receptor
Tregs	Regulatory T lymphocytes
uPAR	Urokinase receptor
UV	Ultraviolet rays
VEGF	Vascular endothelial growth factor
XIAP	X-linked inhibitor of apoptosis protein

CHAPTER 1

INTRODUCTION

Cell-mediated and humoral immune responses are compromised in immunodeficiency disorders and as a result, the ability of the immune system to defend the body from abnormal or invading foreign cells and disease-causing substances is impaired (Halder *et al.,* 2012). This immunocompromised condition predisposes the body not only to the nosocomial infections but also to the opportunistic infections and in addition, increase the susceptibility of developing benign and malignant tumours as a result of decreased cancer immunosurveillance (Dadi *et al.,* 2016). The modulation of immune response in the form of boosting the ability of the body to produce immune cells for the amelioration of disease and cancer susceptibility as well as positive response to conventional cancer radio- and chemotherapy can be achieved by the dietary intake and supplementation of plants materials with established immunomodulatory properties (Gupta *et al.,* 2010; Yin *et al.,* 2017). This is often referred to as "Phytoimmunotherapy" and it's being considered as a new approach for the treatment of cancers (Efferth *et al.,* 2017; Yin *et al.,* 2017). Moreover, many plant products have been exploited for modulation of the immune system in a number of Ayurvedic formulation either alone or in groups (Anwar *et al.,* 2007).

M. oleifera, a tree plant mostly used as part of regular diet in most parts of the world especially in Southeast Asia, Polynesia, India and Africa, has been in ancient scripts, identified as having immune enhancing properties (Anwar *et al.,* 2007). Different parts of the plant (leaves, roots, fruits, flowers, resin and bark) have been reported to possess wide range of pharmacological and therapeutic properties including antitumor, antipyretic, antiepileptic, antispasmodic, anti-inflammatory, diuretic, antiulcer, hypotensive, hypolipidemic, hypoglycemic, hepatoprotective, antifungal and antibacterial activities (Bharali *et al.,* 2003; Leelavinothan *et al.,* 2007; Saini *et al.,* 2016). The polyphenolic constituents of *M. oleifera* leaves, stem, roots, and flowers have been investigated using comprehensive analytical techniques ranging from Liquid Chromatography Mass Spectrometry LC-MS (Bennett *et al.,* 2003), to High Performance Liquid Chromatography HPLC (Atawodi *et al.,* 2010; Vongsak *et al.,* 2013). These investigations have revealed several phytochemicals present in the *M. oleifera* plant. The leaves, however, have mainly flavonoids quercetin and kaempferol (mostly in their glycated form, i.e. isoquercitin and astragalin), chlorogenic acid as well as other phytochemicals like benzylamine (moringine), niazirin and niazirinin (Shanker *et al.,* 2007; Velaga *et al.,* 2017).

Previous studies have shown that pharmacological agents and naturally occurring food chemicals such as the flavonoids and other polyphenols can modify immune system as they have been shown to affect the function of T cells, B cells, NK cells, macrophages, mast cells, basophils, neutrophils, eosinophils and platelets (John *et al.,* 2011; Somerville *et al.,* 2016). Additionally, the leaves of *M. oleifera* being a

rich source of flavonoids, chlorogenic acid and many vital phytochemicals (Mishra *et al.,* 2017), are expected to exhibit immunomodulatory properties capable of enhancing the proliferation of normal lymphocytes and exerting anti-tumour activity. Although the anti-tumour activity of extracts of *M. oleifera* leaves have been explored by analysing its ability to induce apoptosis in proliferating cancer cells (Sreelatha *et al.,* 2011; Tiloke *et al.,* 2016; Tragulpakseerojn *et al.,* 2017), very few studies have investigated the immunomodulatory effect of *M. oleifera* leaves. With the exception of few animal studies, reporting increase in white blood cell or splenocyte count following treatment with extracts of *M. oleifera* leaves, (Gupta et al., 2010; Mousa et al., 2017; Nfambi et al., 2015), close examination of the interactions between the extracts of *M. oleifera* leaves and immune cells, especially lymphocytes within controlled in vitro cultures remained unexplored. To address this research gap, the present study evaluated the effect of 70% ethanolic extract of *M. oleifera* which is mainly comprised of polyphenols on normal and malignant lymphocytes. The cytotoxicity of *M. oleifera* extract on lymphocyte-derived tumour cell lines, and healthy peripheral blood mononuclear cells were tested along with the cell cycle progression, cell proliferation, and apoptosis assays. Both negative and positive impacts of *M. oleifera* on these cells were further deciphered through the profiling of cytokines and apoptotic proteins using customised proteome-antibody arrays. Based on the inputs from detailed arrays of proteins, a panel of signalling pathways were identified which could serve as the possible mechanisms that exploit by *M. oleifera* to deliver its pharmacological effects.

1.1 Problem statement

Infectious diseases, cardiometabolic disorders as well as tumours and cancers are the most prevalent life-threatening conditions in the world today. These conditions target, destroy and/or compromise the overall immune system, leaving the body susceptible to the opportunistic infections among many others. The key to the prevention and treatment of these disease conditions is the strengthening of the immune system using most importantly, readily available, native plant materials with immune boosting properties.

1.2 Study justification

M. oleifera, a widely known herb in Malaysia and throughout South-East Asia, could be ideal for providing a panacea to the identified problem. However, with very few studies have been conducted to explore the immunomodulatory potentials of *M. oleifera* leaves, there is need to carry out an analytical assessment on its ability to exert immunomodulatory activities on normal and tumour-derived lymphocytes. The findings from this study would provide the scientific and laboratory-based evidence for the development and use of *M. oleifera* leaves' supplements in improving the immune system amongst aged and immunocompromised individuals as well as support the current trend in the immunotherapeutic approaches towards the fight against cancer and tumours.

1.3 Null hypothesis

M. oleifera leaves' ethanol extract (MOETE) has no immunomodulatory effect on normal PBMCs and leukaemic cell lines.

1.4 Objectives

1.4.1 General objective

To investigate the immunomodulatory activity of *M. oleifera* leaves' ethanol extract (MOETE) on normal and malignant lymphocytes.

1.4.2 Specific objectives

i. To extract, analyse and identify the phytochemical constituents of MOETE.
ii. To assess the impact of MOETE on cell viability, cell proliferation, cell cycle progression and apoptosis of normal lymphocytes (PBMCs) and leukaemic cell lines (BV173 and Jurkat cells).
iii. To determine the effect of MOETE on cytokine and chemokine secretome of the leukaemic cell lines (BV173 and Jurkat cells).
iv. To evaluate the effect of MOETE on the expression of apoptosis mediators in the leukaemic cell lines (BV173 and Jurkat cells).

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