UNIVERSITI PUTRA MALAYSIA

IN VITRO AND IN VIVO ANTI-LUNG CANCER PROPERTIES OF LEAF ETHANOLIC EXTRACT OF MORINDA CITRIFOLIA L.

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By

LIM SWEE LING

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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Chair: Professor Suhaila Mohamed, PhD
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Lung cancer causes 1.4 million deaths and 1.6 million new cases annually, worldwide. The non-small-cell lung cancer (NSCLC) represents 75% – 80% of lung cancer cases. *Morinda citrifolia* leaves (a common tropical vegetable) scopoletin and epicatechin rich extract (MLE) were assessed for anti-lung cancer effects *in vitro* on A549 NSCLC cells and *in vivo* on BALB/c mice. Cell death was assessed by MTT, caspase assays, cell cycle and fluorescence microscopy. The lung cancer was induced by subcutaneously injecting A549 cells into the back of BALB/c mice. The MLE inhibited the proliferation and induced apoptosis in A549 cells (IC_{50} = 23.47 µg/mL), arrested cancer cell cycle at G0/G1 phases and significantly increased caspase-3/-8 without changing caspase-9 levels. It was not cytotoxic on non-cancerous MRC-5 lung cells even at 100 μg/mL. The orally administered MLE significantly upregulated the pro-apoptotic *P53* genes and downregulated the pro-tumourigenesis genes (*BIRC5*, *JAK2/STAT3/STAT5A*) in the tumour tissues.

Cancer development is closely associated with inflammation, oxidative stress and uncontrolled cell growth. The effects of the MLE containing scopoletin (2.2%) and epicatechin (3.4%), on inflammation, endogenous antioxidant responses and apoptosis-related genes expression in lung-cancer induced mice, compared with the anti-cancer drug Erlotinib were investigated. NSCLC-induced BALB/c mice were fed with 150 and 300 mg/kg MLE and compared with Erlotinib (50 mg/kg body-weight) for 21 days. It significantly increased the anti-inflammatory *IL4*, *IL10* and *NR3C1* expressions in the lung and hepatic tissues, enhanced the *NFE2L2*-dependent antioxidant responses against oxidative injuries and elevated the serum neutrophils. It suppressed inflammation and oedema, while up-regulated the endogenous antioxidant responses and apoptosis genes to suppress the metastasized cancers.

The MLE significantly increased blood lymphocytes counts, spleen tissues B cells, T cells and natural killer cells, and reduced the epidermal growth factor receptor (*EGFR*) which is a lung adenocarcinoma biomarker. The MLE also suppressed the

cyclooxygenase 2 (*COX2*) inflammatory markers; and enhanced the tumour suppressor gene (phosphatase and tensin homolog, *PTEN*). The MLE inhibited the tumour growth cellular genes (transformed mouse 3T3 cell double minute 2 (*MDM2*), V-raf-leukemia viral oncogene 1 (*RAF1*), and mechanistic target of rapamycin (*MTOR*)) mRNA expressions.

Cancer development is also related with angiogenesis and metastasis. The anti-angiogenesis and anti-metastasis properties of MLE were investigated and compared with Erlotinib. The 300 mg/kg body-weight MLE was 41% more effective than 50 mg/kg body-weight Erlotinib in suppressing the lung tumor growth; down-regulating new tumour-related blood vessel development or angiogenesis-relevant genes (*VEGFA*; *AKT1*; *BCL2*; *MAP3K14* and *MAPK1)* in both the liver and lung tissues. The MLE suppressed lung and liver cancer invasive migration or metastasis via down-regulating angiogenesis biochemical pathways (*EGFR*, *MMP9* and integrin).

The 300 mg/kg body-weight MLE significantly (and dose-dependently) suppressed lung tumour growth, more effectively than the 50 mg/kg body-weight Erlotinib treatment for most of the parameters measured. Part of the mechanisms involved enhancing immune responses, suppressing proliferation and interfering with various tumour growth signalling pathways, angiogenesis and metastasis in both the lung and liver tumours.

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

SIFAT-SIFAT ANTI-KANSER PEPARU PADA DAUN *MORINDA CITRIFOLIA* L. ETANOL EKSTRAK *IN VITRO* DAN *IN VIVO*

Oleh

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Pengerusi: Professor Suhaila Mohamed, PhD
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Kanser peparu menyebabkan 1.4 juta kematian dan 1.6 juta kes baru di seluruh dunia setiap tahun. Kanser peparu bukan sel kecil (NSCLC) mewakili 75% - 80% semua kes kanser peparu. Ekstrak daun mengkudu (*Morinda citrifolia)* (MLE) yang kaya kandungan scopoletin dan epicatechin dinilai untuk kesan anti kanser peparu *in vitro* pada sel A549 NSCLC dan *in vivo* pada tikus BALB/c. Kematian sel telah dinilai melalui asai MTT, caspase, kitaran sel dan pemerhatian menggunakan mikroskop pendarfluor. MLE menghalang proliferasi dan apoptosis teraruh dalam sel A549 (IC_{50} = 23.47 μg/mL);menghentikan kitaran sel kanser di fasa G0/G1 dan meningkatkan dengan ketara ekspresi caspase-3/-8 tanpa mengubah ekspresi caspase-9. Ia tidak sitotoksik pada sel peparu sihat MRC-5 walaupun pada tahap 100 μg/mL. Pengambilan MLE melalui mulut dapat meningkatkan regulasi gen penggalak-apoptosis *P53* dengan ketara dan merencat regulasi gen penggalak-kanser (*BIRC5*, *JAK2/STAT3/STAT5A*) dalam kanser peparu tisu.

Pertumbuhan kanser berkait rapat dengan keradangan tisu, tekanan oksidatif dan pertumbuhan sel tidak terkawal. Kesan MLE yang mengandungi scopoletin (2.2%) dan epicatechin (3.4%), ke atas keradangan tisu, tindakbalas antioksidan endogen dan gen apoptosis dalam kanser peparu tikus, telah dibandingkan dengan ubat kanser Erlotinib. Kanser peparu telah diaruh dalam tikus BALB/c dengan menyuntik sel A549 di bawah kulit bahagian belakang tikus. Tikus dirawat dengan diberi makan 150 atau 300 mg/kg MLE dan dibandingkan dengan rawatan Erlotinib (50 mg/kg berat-badan) selama 21 hari. MLE dapat meningkatkan sytokin penghalang-radang *IL4*, *IL10* dan *NR3C1* dalam tisu kanser (peparu dan hati) dengan ketara. MLE juga meningkatkan tindakbalas antioksidan endogen *NFE2L2* untuk memelihara dari kecederaan oksidatif sambil meningkatkan kandungan neutrofil dalam darah. MLE dapat merencat keradangan tisu dan pembengkakan, serta meningkatkan tindakbalas kawal-selia antioksidan endogen dan gen penggalak apoptosis untuk menekan kanser dari merebak.

MLE dapat meningkatkan sistem pertahanan badan dengan ketara terbukti melalui peningkatan sel limfosit darah, sel B tisu limpa, sel T dan sel pembunuh semula jadi; serta mengurangkan reseptor faktor pertumbuhan epidermal (*EGFR*) yang merupakan penanda-bio adenokarsinoma peparu. MLE juga merencat penanda radang cyclooxygenase 2 (*COX2*); dan meningkatkan gen penindas tumor (phosphatase dan tensin homolog, *PTEN*). Rawatannya juga merencat ungkapan mRNA gen berkaitan perbiakan sel kanser (transformed mouse 3T3 cell double minute 2 (*MDM2*), V-raf-leukemia viral oncogene 1 (*RAF1*), and mechanistic target of rapamycin (*MTOR*)) dalam tisu.

Pembiakan kanser juga berkait rapat dengan angiogenesis (pembangunan saluran darah baru) dan metastasis (penhijrahan merebak ke tisu baru). MLE pada dos 300 mg/kg berat badan adalah 41% lebih berkesan daripada 50 mg/kg berat badan Erlotinib untuk menekan pertumbuhan kanser peparu; melalui penekanan gen kawal-selia angiogenesis (*VEGFA; AKT1; BCL2; MAP3K14* dan *MAPK1*) dalam kedua-dua tisu kanser peparu dan hati. MLE juga merencat kanser dari merebak melalui penurunan-kawal-selia laluan biokimia angiogenesis *EGFR*, *MMP9* and integrin, dalam tisu-tisu kanser.

MLE pada dos 300 mg/kg berat badan berkesan merencat pertumbuhan kanser peparu bergantung mengikut dos dengan lebih mujarab daripada 50 mg/kg berat badan rawatan Erlotinib bagi kebanyakan parameter yang dikaji. Sebahagian daripada mekanisme yang terlibat adalah melalui peningkatan tindakbalas imun, penekanan percambahan saluran darah serta mengganggu pelbagai laluan isyarat pertumbuhan tumor, angiogenesis dan metastasis dalam kanser peparu.

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I certify that a Thesis Examination Committee has met on 24th June 2015 to conduct the final examination of Lim Swee Ling on her thesis entitled "*In Vitro* and *In Vivo* Anti-Lung Cancer Properties of Leaf Ethanolic Extract Of *Morinda Citrifolia*" 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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AKT	Protein kinase B
ALK	Anaplastic lymphoma kinase
AO	Acridine Orange
APAF-1	Protease-activating factor 1
ASA	American Society of Anesthesiologists
BAC	Bronchioloalveolar carcinoma
BAD	BCL2-associated agonist of cell death
BAK	BCL2 antagonist/killer (BAK)
BAX	BCL2-associated protein X
BCL2	B cell lymphoma 2
BCL-XL	B cell lymphoma extra large
bFGF	Basic fibroblast growth factor
BH	BCL2 homology
BID	BH3-interacting domain death agonist
BIM	BCL2-interacting mediator of cell death
BIRC5	Baculoviral IAP repeat-containing 5
CD	Cluster of differentiation
CTL	Cytotoxic T lymphocytes
COX	Cyclooxygenase
DISC	Death-inducing signal complex
ECM	Extracellular matrix
EGF	Epidermal growth factor
EGFR	Epidermal growth factor receptor
EML4	Echinoderm microtubule-associated protein-like 4
ErbB	Erythroblastic leukemia viral oncogene homolog
ERK	Extracellular signal-regulated kinases
FAK	Focal adhesion kinase
FISH	Fluorescent in situ hybridization
GM-CSF	Granulocyte-macrophage colony-stimulating factor
GRB2	Growth factor receptor bound protein 2
HER	Human epidermal growth factor receptor
IFN	Interferon
IGF1R	Insulin-like growth factor-I receptor
IHC	Immunohistochemistry
IL	Interleukin
JAK	Janus tyrosine kinase
KRAS	V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog
LLC	Lewis lung peritoneal carcinoma
LPL	Lipoprotein lipase
MAP2K1	Dual specificity mitogen-activated protein kinase kinase 1
MAPK	Mitogen-activated protein kinase
MCHC	Mean cell hemoglobin concentration
MCL-1	Myeloid leukemia cell differentiation protein
MCV	Mean corpuscular volume
MDM2	Transformed mouse 3T3 cell double minute 2
MEK	Mitogen-activated protein kinase kinase
MHC	Major histocompatibility complex
MMP9	Matrix metalloproteinase 9
MOMP	Mitochondrial outer membrane permeabilization

MTOR	Mechanistic target of rapamycin
N	Node
NCCN	National comprehensive cancer network
NCR	Natural cytotoxicity receptor
NFE2L2	Nuclear factor, erythroid derived 2, like 2
NK	Natural killer
NNK	Nicotine-derived nitrosamine ketone
NR3C1	Nuclear receptor subfamily 3, group C, member 1
NSCLC	Non-small-cell lung cancer
PDK	Pyruvate dehydrogenase kinase
PFS	Progression-free survival
PI3K	Phosphatidyl-inositol 3-kinase
PIP3	Phosphatidylinositol (3,4,5) tris-phosphate
PTEN	Phosphatase and tensin homolog
RAF	V-raf 1 murine leukemia viral oncogene homolog 1
RAS	Retrovirus-associated DNA sequences
SCC	Squamous cell carcinoma
SCLC	Small-cell lung cancer
SMAC	Second mitochondria-derived activator of caspases
SOS	Son-of-sevenless
STAT	Signal transducers and activators of transcription
TCR	T-cell receptor
TGFα	Transforming growth factor alpha
Th	T helper
TKI	Tyrosine kinase inhibitor
TNF	Tumor necrosis factor
TRP53	Transformation related protein 53
VC	Vinyl carbamate
VEGF	Vascular Endothelial Growth Factor

CHAPTER I

INTRODUCTION

1.1 Background of study

Lung cancer is the leading cause of cancer-related death worldwide, killing an estimated 1.4 million people annually (Ferlay *et al.*, 2010). In 2030, there will be an estimated 219,440 new cases and 159,390 deaths due to lung cancer (Jemal *et al*., 2011). In Malaysia, lung cancer is, in overall, the third commonest cancer, the commonest tumor to afflict males and the most common cause of cancer deaths accounting for 19.8% of all medically certified cancer related mortality (Al-Naggar and Kadir, 2013), where it accounts for 13.8% of all cancers in males and 3.8% of all cancers in females (Liam *et al.*, 2006). Due to this alarming statistic, it is necessary to develop not only new but also effective means of treatment.

Lung cancer is classified into two major groups: small cell lung carcinoma (SCLC) and non-small cell lung carcinoma (NSCLC). NSCLC usually spreads to different parts of the body more slowly than SCLC, and accounts for more than 85% of lung cancer cases, of which adenocarcinoma (~40% of cases) is the most common subtype, followed by squamous cell carcinoma (SCC) (~25-30%) and large-cell carcinoma (~10-15%) (Wood *et al*., 2014). These subtypes differ in terms of site of origin and patient characteristics, SCC being associated with smoking and origin from bronchial epithelial cells, whilst adenocarcinoma is mainly derived from alveolar/bronchial cells (Langer *et al.*, 2010). In most cases, lung cancer is diagnosed at an advanced stage when treatment outcomes are unfavorable (Mazzone *et al.*, 2007). Not surprisingly, the overall 5-year survival rate for all stages of NSCLC is only 17% (American Cancer Society, 2013). Once recurred or metastasized, the disease is essentially incurable with survival rates at 5 years of less than 5%, and this has improved only marginally during the past 25 years (Jemal *et al*., 2010).

In NSCLC, epidermal growth factor receptor (EGFR) is over-expressed in a substantial proportion of tumors in the range of 40% to 80% and has been associated with a poor prognosis (Silvestri and Rivera, 2005), and it was one of the molecules that was recognized as a biomarker for the development of targeted therapies (Mendelsohn, 2003). Erlotinib, one of the oral EGFR tyrosine-kinase inhibitors (TKIs), has been reported to be effective in second- and third-line therapy (Reck *et al*., 2010; Shepherd *et al*., 2005), and furthermore in first-line (Zhou *et al*., 2011) and maintenance settings (Cappuzzo *et al*., 2010). Therefore, Erlotinib has been approved in more than 80 countries for the treatment of advanced NSCLC, and was also approved in the People's Republic of China (PRC) in 2006 and USA in 2004 (Cohen *et al*., 2010). However, the drawbacks of Erlotinib has been reported, such as skin rash, acne, diarrhea, headache, mucositis, hyperbilirubinemia, neutropenia and anemia (Ranson, 2004).

Moreover, chemotherapy was reported to cause undesirable side-effects, severe damage to normal cells and resistance development to the agents (Mohan *et al*., 2011). Due to the poor respond of chemotherapy, limited effective drug, negative side effects of medication, and negative social impacts, a dire need for an alternative treatment for lung cancer patients.

Currently, much attention has been placed on anticancer drugs of herbal origin. They demonstrate selective toxicity toward tumorigenic tissues by suppressing proliferation, triggering apoptosis, inhibiting angiogenesis, and retarding metastasis in both *in vitro* and *in vivo* (Tan *et al*., 2011). For example, Paclitaxel (Taxol), a natural compound isolated from the Pacific northwest yew tree, is used for the treatment of lung cancer (Bonomi, 1999).

One of the most beneficial plants in the tropical areas, which has been flourishingly planted is *Morinda citrifolia* L (Rubiaceae), known popularly as noni, a small evergreen tree or shrub, native to South Asia that currently grows throughout the tropics, has been utilized as a remedy for >2000 years by Polynesians (Kinghorn *et al*., 2011). The need of *M. citrifolia* increases due to importance of widely curative influences such as anticancer, antioxidant, antibacterial, hypertensive, anti-inflammatory and antimicrobial (Alsaeed, 2013). *M. citrifolia* leaves ethanolic extract have antioxidant, liver-protective and wound healing effects (Nayak *et al*., 2009) without any acute, sub-acute and sub-chronic oral toxicity (West *et al*., 2007). An oral intake of 1000 mg/kg of *M. citrifolia* leaf 50% ethanolic extract has been reported as the no observed-adverse-effect level (NOAEL) (Lagarto *et al*., 2013). *M. citrifolia* leaf dichloromethane extract reportedly has *in vitro* antiproliferative activities in KB (human epidermoid carcinoma) and HeLa (human cervical carcinoma) cell lines (Thani *et al*., 2010), thus indicating its general anti-cancer potential, but there is no report on its anti-lung cancer effects or the mode of action.

This study can potentially reduce the numbers of death, providing cheaper medicine drug due to its bioavailablity in Malaysia, and without negative side effects on lung cancer patient. Consequently, it may contribute to the improvement of quality of life, as well as economic and social well being of Malaysia.

1.2 Hypothesis

It is hypothesized that *M. citrifolia* leaves 50% ethanolic extract (MLE) will show cytotoxic effect on the human lung adenocarcinoma cell line (A549), without affecting the human lung fibroblast cell line (MRC5), and will has antiproliferative effect on animal lung cancer model via immune-mudulatory and anti-angiogenesis/anti-metastasis signaling pathways.

1.3 Aims of the study

General Objectives : To determine the *in vitro* and *in vivo* anti-lung cancer activities of ethanolic extract of *Morinda citrifolia* leaves

Specific Objectives :

1. To identify the chemical profile of MLE
2. To evaluate *in vitro* cytotoxic effects of MLE on MRC5 and A549 cells
3. To determine the immono-modulation exhibited by the MLE on A549-induced BALB/c mice
4. To determine the anti-angiogenesis/anti-metastasis signaling pathway and pathological changes exhibited by the MLE on A549-induced BALB/c mice

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