UNIVERSITI PUTRA MALAYSIA

CHARACTERIZATION AND ANTI-CANCER EFFECTS OF CITRALLOADED NANOSTRUCTURED LIPID CARRIER IN BREAST CANCER CELLS In vitro AND In vivo

NORAINI NORDIN

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By

NORAINI NORDIN

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

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DEDICATION

This thesis is dedicated to:

My beloved parents Mr.Nordin Abu and Mrs.Selamah Musa for their love, support, endless encouragement and unrelenting faith in my ability to accomplish this PhD journey. You both are absolutely the most perfect parent in this whole wide world.

My lifelong partner cum my best friend, Zarul Hafiz Rashidi for all his love and tireless moral support, who believed in me and truly is the greatest blessing from Allah.

Abstract of thesis presented to Senate of Universiti Putra Malaysia in fulfillment of the requirement for the degree of Doctor of Philosophy

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Chairman : Associate Professor Noorjahan Banu bt Mohamed Alitheen, PhD
Faculty : Biotechnology and Biomolecular Science

Breast cancer is a life-threatening health issue in women globally. Metastasis has been attributed as a key factor for the increase in cancer-related deaths. Innovative research elucidatinga possible cure for cancer via inhibition of metastatic ability has received considerable interest. However, although various cancer therapeutic such as chemotherapy are useful, their unmanageable side effects still remain unresolved. To address this issue, cancer nanotherapy has been utilized to establish a novel drug delivery system for anticancer agents. Nanostructured lipid carrier is one of the systems that still under investigation due to its applicability. Citral (*Cymbopogon citratus*), a member of essential oil family is mainly derived from the extraction of lemongrass which is popular in pharmaceutical, food, perfume and cosmetic industries. Studies showed that citral has anti-proliferative properties on several cancers including breast cancer. Citral is a poor aqueous solubility compoundthat has been studied to inhibit cancer developments. In this study, it is postulated that the incorporation of citral into nanostrucuted lipid carrier (NLC) will improve solubility and delivery of the compound while not compromising its therapeutic effects. Thus, the objective of the current study is to characterize the formulation of nanostructured lipid carrier loaded with citral and to evaluate its anti-cancer effects in MDA MB-231 cells *in vitro* and on breast cancer cells 4T1 in murine mice model. Notably, citral was loaded into the NLC using high pressure homogenization methods. Characterization of NLC-citral was determined using Transmission Electron Microscope (TEM), zeta potential, drug loading and drug release studies. TEM and zeta sizer analyses revealed that NLC-citral is a nano size particle with an average diameter size of 54.12 ± 0.30 nm. Meanwhile, zeta potential of NLC-citral was -12.73 ± 0.34 mV with an entrapment efficiency of 98.9 ± 0.124%, and drug loading was 9.84 ± 0.041%. No mortality, toxic signs and changes of serum biochemical profile observed in the healthy mice after being exposed with NLC-citral for 28 days via oral administration.In addition, through flow cytometry cell cycle analysis, Annexin V analysis, JC-1 and fluorometric assays, it was shown that NLC-citral managed to induce G2/M arrest and induced apoptosis in

MDA MB-231 cells. Besides, the percentage of cells in G2/M arrest also increased in NLC-citral in a concentration dependent manner. Furthermore, a prominent anti-metastatic ability of NLC-citral was demonstrated in *in vitro* scratch, migration and invasion assays. A significant reduction of migrated and invaded cells was observed in the NLC-citral treated MDA MB-231 cells. To further evaluate apoptotic and anti-metastatic mechanism of NLC-citral at the molecular level, microarray-based gene expression profiling and proteomic profiling were conducted. Based on the result obtained, NLC-citral was found to regulate several important signaling pathways related to cancer development such as apoptosis, cell cycle and metastasis signaling pathways. Results obtained from gene expression analysis were validated through the targeted RNA sequencing and real time polymerase chain reaction. Subsequently, this observation was tested*in vivo* in a murine model utilizing murine breast cancer 4T1 cells using BALB/c mice. Treatment using NLC-citral significantly led to a reduction of tumor size inthe treated mice. Outcomes of histopathology and TUNEL analyses showed that the number of cancer cells in the tumor decreased 28 days post oral treatment with NLC-citral (3.5-fold). Furthermore, proteomic profiling and real time polymerase chain reaction confirmed anti-tumor effects of NLC-citral*in vivo*. In conclusion, the NLC-citral system inhibited the proliferation of breast cancer cells *in vitro* and *in vivo*, majorly through the induction of apoptosis, reduction of inflammation, activation of anti-angiogenesis and anti-metastasis potential. This study shows that loading of citral into NLC did not alter the therapeutic potential of citral and the NLC-citral is a promising and effective anticancer agent for breast cancer therapeutics.The NLC thus has excellent potential to be developed into a drug-carrier and delivery system for the treatment of cancers.

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

PENCIRIAN PEMBAWA LIPID BERNANOSTRUKTUR TERISI CITRAL DAN KESAN ANTI KANSERNYA SECARA *In vitro* DAN *In vivo* TERHADAP SEL KANSER PAYUDARA (MDA MB-231 DAN 4T1)

Oleh

NORANI NORDIN

Jauuari 2017

Pengerusi : Profesor Madya Noorjahan Banu Bt Mohamed Alitheen, PhD
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Kanser payudara merupakan isu kesihatan yang mengancam nyawa dalam kalangan wanita seluruh dunia.Metastasis adalah penyumbang utama dalam peningkatan bilangan kematian disebabkan kanser.Kajian inovatif bagi penyembuhan kanser melalui perencatan keupayaan metastasis telah mendapat perhatian besar dalam kalangan penyelidik. Walaupun, terdapat pelbagai rawatan kanser yang berguna seperti terapi kimia, namun masih terdapat kesan sampingan tidak terurus yang serius. Sebagai penyelesaian, terapi nano kanser telah digunakan secara efektif untuk mewujudkan sistem penyampaian ubat yang baru sebagai ejen anti kanser.Pembawa lipid bernanostruktur ialah salah satu sistem yang masih dikaji kebolehannya.Citral *(Cymbopogon citratus)* merupakan antara salah satu daripada minyak pati yang diperoleh daripada pengekstrakan serai dan terkenal dalam industri farmaseutikal, makanan, haruman dan kosmetik.Gabungan minyak pati dalam terapi kanser merupakan bidang kajian yang baru.Projek ini bertujuan untuk mencirikan formulasi pembawa lipid bernanostruktur terisi Citral bagi menentukan kesan anti kansernya secara *in vitro* kepada sel MDA MB-231.Selain itu, untuk menilai kesan anti tumornya secara in vivo terhadap kanser sel kanser payudara 4T1 ke atas model tikus.Citral telah dimuatkan kedalam pembawa lipid bernanostruktur menggunakan kaedah penyeragaman tekanan tinggi.Pencirian pembawa lipid bernanostruktur-Citral (NLC-Citral) telah ditentukan menggunakan kajian mikroskop elektron pancaran (TEM), keupayaan zeta, pemuatan ubat dan pelepasan ubat. Analisis TEM dan keupayaan saiz zeta telah mendedahkan bahawa pencirian pembawa lipid bernanostruktur-Citral mempunyai partikel bersaiz nano dengan purata diameter 54.12 ± 0.30 nm. Sementara itu, keupayaan zeta bagi NLC-Citral adalah -12.73 ± 0.34 mV dengan kecekapan pemerangkapan 98.9 ± 0.124%, dan pemuatan ubat adalah 9.84 ± 0.041%. Tiada kematian, kesan toksin dan perubahan profil serum biokimia kelihatan dalam tikus yang sihat setelah 28 hari menerima NLC-Citral secara oral. Tambahan lagi, dengan menggunakan analisis kitaran sel, analisis annexin V, analisis JC-1 dan analisis caspase 8/9 assai telah menunjukkan bahawa NLC-Citral berjaya mencetuskan

penahanan di fasa G2/M dan juga mencetuskan apoptosis. Selain itu, peratusan sel dalam penahanan G2/M juga turut meningkat berdasarkan kepekatan NLC-Citral.Keupayaan anti metastasis telah menunjukkan kesan yang menonjol dalam assai penyembuhan luka, migrasi dan invasi.Sel MDA MB-231 yang diberi rawatan NLC-Citral menunjukkan pengurangan ketara dalam bilangan sel migrasi/invasi.Untuk menilai mekanisma apoptosis dan anti metastasis NLC-Citral pada tahap molekular, mikroarray dan profil protin telah dijalankan.Berdasarkan keputusan yang diperolehi, NLC-Citral telah ditemui dapat mengawal selia beberapa jalan isyarat yang berkaitan dengan pertumbuhan kanser seperti apoptosis, kitaran sel, dan metastasis. Keputusan daripada ekspresi gen telah disahkan melalui 'targeted RNA sequencing' dan Real Time PCR analisis. Seterusnya, pemerhatian ini telah diuji secara *in vivo* dalam model tikus.Rawatan menggunakan NLC-Citral menunjukkan pengurangan ketara bagi saiz tumor dalam tikus yang dirawat.Keputusan daripada analisis histopatologi dan TUNEL mendedahkan pengurangan bilangan sel kanser dalam tumor setelah diberi rawatan NLC-Citral (3.5-fold) secara oral selama 28 hari.Akhir sekali, profil proteomic dan Real Time PCR mengesahkan kesan anti-tumor NLC-Citral secara *in vivo*.Kesimpulannya, sistem NLC-Citral menghalang proliferasi sel kanser payudara secara in vitro dan in vivo melalui induksi apoptosis, pengurangan keradangan serta pengaktifan keupayaan anti-angiogenesis dan anti metastasis.Kajian ini menunjukkan bahawa pemuatancitral ke dalam NLC tidak menjejaskan potensi citral terhadap sel barah payu dara. Ini membuktikan NLCmempunyai potensi yang unggul untuk dikembangkan sebagai sistem pembawa dan penghantar ubatan dalam rawatan kanser.

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I certify that a Thesis Examination Committee has met on 17 January 2017 to conduct the final examination of Noraini binti Nordin on her thesis entitled "Characterization and Anti-Cancer Effects of Citral-Loaded Nanostructured Lipid Carrier in Breast Cancer Cells *In Vitro* and *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 Master of Science. 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
APC	Antigen-presenting cells
AST	Aspartate Aminotransferase
ATCC	Animal Tissue Culture Collection
BAX	Bcl-2 Associated X-Protein
CDK	Cyclin Dependent Kinase
cDNA	Complementary DNA
COX-2	Cyclooxygenase 2
CXCL	Chemokine Ligand
DL	Drug Loading
DMEM	Dulbecco's Modified Eagle Medium
DMSO	Dimethyl sulfoxide
DMSO	Dimethyl sulfoxide
ECM	Extracellular Matrix Formation
EDTA	Ethylenediaminetetraacetic acid
EE	Entrapment Efficiency
FACS	Fluorescence-activated cell sorter
FITC	Fluorescent isothiocyanate
FZD-8	Frizzled-8
GAPDH	Glyceraldehyde 3-phosphate dehydrogenase
GJIC	Gap Junction Intercellular Communication
HEGF	Human Endothelial Growth Factor
HPO	Hydrogenated Palm Oil
HRP	Horsedish peroxidase
IC_{50}	Half maximal inhibitory concentration

IC_{50}	Half maximal inhibitory concentration
ICAM-1	Intercellular adhesion molecule
IFN-γ	Interferon-gamma
IL-10	Interleukin-10
IL-1β	Interleukin-1 beta
IL-1β	Interleukin-1 beta
IL-2	Interleukin-2
iNOS	Inducible nitric oxide synthase
JC-1	5,5′,6,6′-tetrachloro-1,1′,3,3′-tetraethylbenzimidazolylcarbocyanine iodide
M-CSF	Macrophage colony stimulating factor
MDA	Malondialdehyde
MMP	Matrix metalloproteases
MRNA	Messenger RNA
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
NaCl	Sodium chloride
NCBI	National Centre for Biotechnology Information
NCBI	National Centre for Biotechnology Information
NFK-β	Nuclear Factor Kappa Light chain enhancer activated B cells
NGS	Next generation sequencing
NGS	Next generation sequencing
NIC	The National Cancer Institute
NK	Natural killer
NO	Nitric oxide
PBS	Phosphate buffer saline
PCR	Polymerase chain reaction
PI	Propidium Iodide
PTEN	Phosphatase and Tensin

PTX	Paclitaxel
PXDN	Peroxidasin
QD	Quantum Dot
RNA	Ribonucleic acid
RNAse	ribonuclease
RNAse	ribonuclease
ROBO1	Cell adhesion Receptor
ROS	Reactive Oxygen Species
RT-QPCR	Real Time quantitative PCR
SLN	Solid Lipid Nanoparticle
TEM	Transmission Electron Microscope
TGF-β	Tumor Growth Factor-beta
TIL	Tumor infiltrating lymphocytes
TIMP	Tissue Inhibitor of Metalloproteinase
TNBC	Triple Negative Breast Cancer
TNF-α	Tumor Necrosis Factor-alpha
TUNEL	Terminal deoxynucleotidyl transferase dUTP nick end labeling
VEGF	Vascular endothelial growth factor
WHO	World Health Organization

CHAPTER 1

INTRODUCTION

Cancer is one of the leading causes of death globally.The increasing occurrence of breast cancer has accounted for 25% of breast cancer related death among Malaysians's female(Youlden et al., 2014).In Malaysia, the number of breast cancer cases among women has steadily increased, with an incidence rate reported to be highest in Chinese, followed by Indians and lastly by Malays (Islam et al., 2015). The incidence and mortality rate attributable to this increase is due to various factors, including late detection, increased risk factorinfluence, as well as lack of viable treatments. Interestingly, in the United States, overall cancer related death has declined in the recent decade due to the early detection and treatment provided; however high number of cancer mortality still exist (Mokdad et al., 2017).

Breast cancer is a heterogeneous disease with majority of the breast cancer mortality is due to the development of distant metastases within only 3 years after the detection of the primary cancer site (Kimbung *et al*., 2015).Metastasis is a process of tumor cells migration and invasion from a primary site to colonize other organs or a secondary site (Steeg, 2016). It is precedes with the cells originated from the primary tumor invading the host tissue through the blood vessels and lymph nodes until the tumor cells move to a distant organs (Scully*et al*., 2012). Considerable work has been developed over the last decades to establish appropriate treatments to circumvent this problem such as chemotherapy, surgery, and various other therapies. However, chemotherapy is laden with long term side-effects that substantially affect the patient's quality of life, including unbearable physical pain, fatigue, bone health and lower survivorship post treatment (Casla *et al*., 2015). Ever since, research to find the best breast cancer therapeutics has focused on preventing an initial metastasis in high-risk patients.

Due to high incidence of cancer nowadays, people are now turning to alternative medicine. It is reported that about 60% of cancer patients use natural products as a complementary and alternative therapy alongside conventional treatments (Sughrue *et al*., 2010). Previously, natural product and its derivatives accounted for 57% of all cancer drugs used in clinical trials of cancers(Cragg & Newman, 2000). Moreover, essential oils have been reported as potential anticancer agents against various types of cancers including breast cancer (Zu *et al*., 2010). Essential oil constituents such as perillyl alcohol have alsobeen reported to progress through clinical trial Phase II in ovarian cancer patients (Bailey *et al*., 2002).

Citral is a key constituent of the lemon-scented essential oil extracted from lemongrass *(Cymbopogoncitratus).*Citral has been previously found to inhibit human breast cancer cells proliferation and induced apoptosis through cell cycle arrest at G2/M phase of MCF-7 cell lines (Chaouki*et al*., 2009). Citral also possesses promising anti-cancer properties towards several hematopoietic cell lines (Dudai*et al*., 2013).

Possible anticancer potency of citral has also been tested synergistically with curcumin against breast cancer cell proliferation (Patel*et al*., 2015). Though citral holds a bright future in cancer therapeutics, it still suffers from some limitations due to its hydrophobic properties (Park*et al*., 2015). Solubility is a crucial parameters to achieve in the development of an effective drug; poorly soluble drugs require high doses of treatment in order to reach desired therapeutic effects (Savjani *et al*., 2012).The improvement of drug solubility is one of the most challenging aspects of drug development process especially for oral administration (Di*et al*., 2012). Recently, nanoparticle have been reported to enhance the solubility and bioavailability of several water soluble drugs (Sharma*et al*., 2016).

The application of nanotechnology in medical research has fundamentally revolutionized specificity of anticancer drugs frequently associated with therapeutic side effects. One of the goals for nanomedicine in pharmaceutics is to advance the system for more effective delivery of anti-cancer therapy and diagnosis (Sadat*et al*.,2015). To date, nanostructured lipid carrier (NLC) has become a novel nano-carrier platform for development of effective drug delivery for cancer chemotherapeutics (Selvamuthukumar & Velmurugan, 2012). NLC has been previously reported to improve bioavailability and solubility in most of the hydrophobic cancer drugs, including Tamoxifen(How *et al*.,2013). In addition, it confers controlled drug release properties and increase chemical stability of the incorporated compound because of its highly unordered lipid matrices, where a high stacking of compounds is achieved (Uner, 2006). Optimally, incorporation of anticancer agents within NLC has been pursued to increase its efficacy while reduce the dose related toxicity (Han *et al*., 2016).Nevertherless, the incorporation of citral in NLC systems is yet to be elucidated, especially for breast cancer therapeutics so far. Thus, this study is aimed to investigate the anticancer and cytotoxicity effects of NLC-citral on human breast cancer cell (MDA MB-231) and 4T1 cell-induced breast cancer in mice. In addition, the safety profile of citral incorporated into the NLC was done to check its toxicity effects on healthy mice.

Hypothesis of the study are:

1. NLC-citral is cytotoxic to human breast cancer cells
2. NLC-citral will induce apoptosis and exhibit anti-metastasis activity in breast cancer cells *in vitro* and *in vivo*.

Main objective

To characterize the synthesized NLC-citral and evaluate its in vitro and in vivo anti-cancer activities on breast cancer cells.

Specific objectives of the study are:

1. To synthesize, perform physicocharacterization and to assess the toxicity profile of NLC-citral
2. To evaluate the *in vitro* cytotoxic effects and anti-cancer potential of NLC-Citral in human breast cancer cell line MDA MB-231 ; and
3. To determine *in vivo* apoptotic and anti metastatic activities of NLC-citral on 4T1 challenged Balb/C mice

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