CYTOTOXIC EFFECTS OF 7-GERANYLOXYCINNAMIC ACID ISOLATED FROM *Melicope lunu-ankenda* (Gaertn) T.G.Hartley LEAVES ON BREAST CANCER CELL LINES (MCF-7 AND MDA-MB-231)

By

ELIASER ENAS MOHAMED ABDAALLAH

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

June 2022

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

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ELIASER ENAS MOHAMED ABDAALLAH

June 2022

Chairman : Associate Professor Ahmad Faizal bin Abdull Razis, PhD
Institute : Bioscience

Breast cancer is the most prevalent form of cancer in women, it has been considered as second causing death after lung cancer, worldwide. Even though a numerous number of anticancer drugs have been applied in clinical practice worldwide, their applications are significantly limited because of its side effects. Therefore, studies have been conducted to develop new anticancer therapeutic agents with low systemic toxicity and selective toxicity to cancer cells. *Melicope lunu-ankenda* is widely distributed in tropical and subtropical countries including Malaysia and it is well known for its biological activities such as antibacterial, antioxidant, analgesic, antidiabetic, and anti-inflammatory. A considerable number of secondary metabolites have been isolated from *M. lunu ankenda* like phenolic acid derivatives, flavonoids, coumarins and alkaloids. However, their underlying anticancer mechanisms of action have not been well investigated, particularly in human cell lines. Hence, the aim of the study was designed to assess the cytotoxic effects of 7-geranyloxycinnamic acid isolated from *Melicope lunu-ankenda* on the human breast cancer cell lines (MCF-7 and MDA-MB-231). In this study the leaves of the plant were collected and extracted using three different solvent systems including methanol, petroleum ether and chloroform. Further extraction steps were performed to isolate the pure compound followed by ^{1}H and ^{13}C NMR for compound elucidation. The cytotoxic effect of the crude extracts were screened among three cancer cell lines (HT-29, HepG2 and MCF-7), the result showed that, the petroleum ether and chloroform crude extracts exhibited strong cytotoxic effect toward HT29 with IC_{50} 20.645±0.023 µg/mL and 19.662±0.0132 µg/mL respectively, while weak cytotoxic effect by methanol crude extract on the same cancer cell lines was observed. Furthermore, moderate cytotoxic effect was recorded for the crude extracts toward HepG2 and MCF-7 cell lines respectively. On the other hand, the 7-geranyloxycinnamic acid which isolated from *Melicope lunu-ankenda* leaves has been tested against MCF-7, MDA-MB-231and HT-29 and it has shown a strong effect on MCF-7 and MDA-MB-231 with IC_{50} values 1.847±0.212 µg/mL and 1.732±0.060 µg/mL in 72 hour incubation respectively. However the compound was found to be not

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toxic toward MCF-10a with IC_{50} 48.814±0.386 µg/mL at the same period of time. Both breast cancer cell lines were chosen to posses the anticancer evaluation. The compound has induced MCF-7 and MDA-MB-231 cells death with distinct characteristics evident confirmed by morphological assessment which exemplified by membrane blebbing, chromatin condensation, late apoptosis and necrosis. The ultrastructure's alteration such as membrane blebbing, cytosolic shredding, chromatin condensation and margination, nuclear convolution, shrinkage of nuclei, and lipid droplet were observed using transmission and scanning electron microscopy. Additionally, Annexin V/PI-flow cytometry assay has shown a significant increase of apoptotic features followed by modulation of caspases activities. It can be concluded that 7-geranyloxycinnamic acid is a potent anticancer agent towards MCF-7 and MDA-MB-231 cancer cell lines via modulation of apoptosis pathways. Further extensive work needed to be done to bring out the therapeutic factors and develop the potential of the compound using several animal model.

Keywords: 7-geranyloxycinnamic acid melicope lunu ankenda, breast cancer, cytotoxicity.

SDG: GOAL 3: Good Health and Well Being.

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

KESAN SITOTOKSIK ASID 7-GERANILOKSISINAMIK TERASING DARIPADA DAUN *Melicope lunu-ankenda* (Gaertn) T.G.Hartley KE ATAS SEL KANSER PAYU DARA (MCF-7 dan MDA-MB-231)

Oleh

ELIASER ENAS MOHAMED ABDAALLAH

Jun 2022

Pengerusi : Profesor Madya Ahmad Faizal bin Abdull Razis, PhD
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Kanser payu dara merupakan kanser yang paling lazim dalam kalangan wanita, ia dianggap sebagai penyebab kedua kematian selepas kanser paru-paru, di seluruh dunia. Walaupun terdapat pelbagai ubat antikanser telah diaplikasikan dalam amalan klinikal di seluruh dunia, penggunaannya secara signifikan adalah terhad disebabkan oleh kesan-kesan sampingan. Oleh sebab itu, kajian ini dijalankan bagi membangunkan agen terapeutik antikanser baharu dengan ketoksikan sistemik yang rendah dan ketoksikan selektif terhadap sel kanser. *Melicope lunu-ankenda* telah tersebar dengan meluas di negara tropika dan subtropika termasuk Malaysia dan ia sangat dikenali kerana aktiviti biologinya seperti antibakteria, antioksidan, analgesik, antidiabetik, dan antiradang. Sebilangan metabolit sekunder yang agak banyak telah diasingkan daripada *M. lunu ankenda* seperti derivatif asid fenolik, flavonoid, kumarin dan alkaloid. Walau bagaimanapun, mekanisme antikanser mereka masih belum diterokai secara meluas, terutamanya di dalam sel manusia. Oleh itu, tujuan kajian ini direka adalah bagi menilai kesan kesitotoksian asid 7-geraniloksisinamik yang diasingkan daripada *Melicope lunu-ankenda* ke atas sel kanser payu dara manusia (MCF-7 dan MDA-MB-231). Dalam kajian ini daun tumbuhan tersebut telah dikumpul dan diekstrak menggunakan tiga sistem pelarut yang berbeza termasuk metanol, petroleum eter dan kloroform. Langkah pengekstrakan selanjutnya telah dijalankan bagi mengasingkan sebatian tulen diikuti oleh analisa ^{1}H dan ^{13}C NMR. Kesan kesitotoksikan bagi ekstrak mentah telah disaring ke atas tiga sel kanser (HT-29, HepG2 dan MCF-7), ekstrak mentah petroleum eter dan kloroform didapati mempunyai kesan sitotoksik yang kuat terhadap HT-29 dengan masing-masing IC_{50} 20.645±0.023 µg/mL dan 19.662±0.013 µg/mL, manakala kesan sitotoksik yang lemah oleh ekstrak mentah metanol ke atas sel kanser yang sama telah dikesan. Tambahan pula, kesan sitotoksik yang sederhana telah direkodkan bagi ekstrak mentah, masing-masing terhadap HepG2 dan MCF-7. Sebaliknya, asid 7-geraniloksisinamik yang diasingkan daripada daun *Melicope lunu-ankenda* dan diuji ke atas MCF-7, MDA-MB-231 dan HT-29 telah menunjukkan kesan yang kuat terhadap MCF-7 dan MDA-MB-231 dengan nilai IC_{50} masing-masing

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1.847±0.212 µg/mL dan 1.732±0.060 µg/mL untuk 72 jam inkubasi. Namun sebatian tersebut telah ditemui tidak toksik terhadap MCF-10a dengan IC_{50} 48.814±0.386 untuk tempoh waktu yang sama. Kedua-dua titisan sel kanser payu dara tersebut telah dipilih untuk melalui penilaian antikanser. Sebatian itu telah mengaruh kematian sel MCF-7 dan MDA-MB-231 dengan ciri yang jelas dibuktikan melalui penilaian morfologi di bawah mikroskop fasa kontras, dan mikroskop fluoresen menggunakan pewarnaan berganda akridina oren dan iodida propidium seperti yang ditunjukkan oleh blebbing membran, pemeluwapan kromatin, apoptosis lewat dan nekrosis. Pengubahan ultrastruktur seperti pembleban membran, pencincangan sitosolik, pemeluwapan kromatin dan marginasi, konvulasi nuklear, pengecutan nukleus, dan titisan lipid telah dikesan menggunakan transmisi dan mikroskopi elektron pengimbas. Di samping itu, asai sitometri Annexin V/PI-flow telah menunjukkan peningkatan apoptotik yang signifikan diikuti oleh modulasi aktiviti caspase. Kajian ini menyimpulkan bahawa asid 7-geraniloksisinamik merupakan agen antikanser berpotensi terhadap sel kanser MCF-7 dan MDA-MB-231 melalui modulasi laluan apoptosis. Kajian lanjutan yang meluas perlu dijalankan untuk mendedahkan faktor-faktor terapeutik dan membangunkan potensi aktif sebatian tersebut menggunakan beberapa model haiwan.

Kata Kunci: asid 7-geraniloksisinamik, melicope lunu ankenda, kancer payudara, sitotoksik.

SDG: MATLAMAT 3: Kesihatan yang Baik dan Kesejahteraan.

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LIST OF ABBREVIATIONS

ATCC	American type culture collection
℃	Degree Celsius
DMSO	dimethyl sulfoxide
DNA	Deoxyribonucleic acid
EDTA	Ethylenediaminetetraacetic acid
FBS	fetal bovine serum
mg	milligram
MHz	Mega hertz
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5- thiazoyl blue tetrazolium bromide
NMR	nuclear magnetic resonance
PBS	phosphate buffer saline
ppm	part per minute
Rpm	revolution per minute
SD	standard deviation
TNM	Tumor Node Metastasis

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CHAPTER 1

INTRODUCTION

1.1 Research background

Breast cancer is one of the most frequent cancer affecting women as over 1 million women worldwide are diagnosed with breast cancer each year. Exploring an alternative protocols in dealing with disease particularly cancer are gaining the global attention. The medicinal plants usage in folk medicine highlights their significance particularly in the management of cancer and other related diseases. They possessed medicinal principles that can improve immunity of the body thereby limiting inflammations and progression of the diseases (Nordin et al., 2018).

With the advancement of research, numerous phytochemical compounds were isolated and elucidated with proven anticancer activities. *Melicope lunu ankend* is widely distributed in tropical parts of Asia. Traditionally, the plant is been used to treat several illnesses including hypertension, menstrual disorder, diabetes, fever, also as an emmenagogue and tonic. Cytotoxicity, antimicrobial, antioxidant, analgesic, antidiabetic, and anti-inflammatory activities reported recently (Abdulwanis et al., 2020).

The plant was subjected to further investigation that lead to the isolation of some compounds with potent activities against some ailments. Therefore, the purpose of this study was to screen the cytotoxicity level of *Melicope Lunau ankenda* crude extacts against the three cancer cell lines (MCF-7, HT29 and HepG2) and as well as to further evaluate the anticancer effect possessed by the pure compound on (MCF-7, MDA-MB-231) cancer cell lines.

1.2 Problem statement

- There are increasing risk of harmful side effects of the standard treatments for cancer like surgery, chemotherapy, and radiology.
- Researchers are interested in the use of compounds that has anticancer potential without undesirable toxic side effects.
- To the current situation, it's clear from literature review that no work has been done involving the anti-cancer properties of *Melicope Lunau ankenda,* it will prove that the endemic Malaysian plants could serve as leads in the search for anti - cancer agent.
- Isolation and elucidation of compound(s) from *Melicope Lunau ankenda* with cytotoxicity to the cancer lines may serve as a lead for an anticancer agent.

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Hypothesis

Null hypothesis (H0)

7-geranyloxycinnamic acid does not protect the *in vitro* MCF-7 and MDA-MB-231 cancer cell line.

Alternative hypothesis (Ha)

7-geranyloxycinnamic acid is a potential inhibitor of tumor cell growth in the *in vitro* MCF-7 and MD-MB-231 cancer cell lines.

1.3 General objective

This study aims to investigate the cytotoxic attributes of 7-geranylecinnamic acid to inhibit cancer cell proliferation and the induction of apoptotic cell death on human breast cancer cell lines.

1.4 Specific objectives

1. To screen the cytotoxicity of crude extract of *Melicope lunu-ankenda* against different cancer cell lines.
2. To isolate, purify and elucidate the 7-geranyloxycinnamic acid from *Melicope lunu-ankenda* leaf extract.
3. To determine the cytotoxicity of the 7-geranyloxycinnamic acid on human breast cancer cell lines and normal cells.
4. To investigate the induction of apoptosis and cell cycle arrest induced by the cytotoxic effect of the 7-geranyloxycinnamic acid.

1.5 Justification

Medicinal plants are gaining more attention and popularity as alternative form of treatment cancer and other related diseases. This is so, because of acceptance, availability and relative safety. *Melicope lunu-ankenda* is one of the plant that is popular amongst Asian use for the management of cancer. It is therefore, justifiable to test the cytotoxicity potential of the 7-geranyloxycinnamic acid isolated from the plant.

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