UNIVERSITI PUTRA MALAYSIA

INFLUENCE OF ANNONA MURICATA LINN POLYMORPHISM ON POLYPHENOLIC PRODUCTION AND ITS ANTI CANCER EFFECTS

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By

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

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Often the conventional drugs had difficulties in combatting cancer mainly due to resistance to treatment and the risk of health setbacks, many has turned to medicinal plant for hope. Active constituents and compounds found in medicinal plant were proven effective in targeting cancer in vitro and in vivo levels while some of them had been subjected to clinical trial. While such findings on the medicinal plants are great and convincing, there is one aspect being overlooked and require as much attention. Given that a medicinal plant from certain place is rich with active compounds that serve the cancer therapeutic criteria, it is not necessarily to be the case for that similar plant found in another location i.e., level of its active compounds content might differ. In the present study, a total of 19 *Annona muricata* Linn (soursop) samples from different location (Peninsular Malaysia states: Johor, Melaka, Negeri Sembilan, Selangor, Perak, and Perlis) were evaluated on the basis of polymorphism influence on the polyphenolic level and cytotoxicity effect in targeting the breast cancer cells. The ISSR-PCR of the DNA samples indicated the presence of polymorphism (72.41%) among the *Annona muricata* Linn samples and was supported by the discrepancies of data results observed in antioxidant level and anti-proliferative assay of the leaf aqueous extract on breast cancer cells (MCF-7, MDA-MB-231, and 4T1). M1 AMCE had the highest content of phenolic (73.2 µg/mL GAE) and flavonoid (191.4 µg/mL CE) and also the highest antioxidant capacity in ORAC assay (254.7 µM) while A1 possessed the highest antioxidant capacity in FRAP assay. Based on the anti-proliferative assay, B1 AMCE was the most potent in killing MCF-7 (IC_{50}= 221.67 µg/mL) and 4T1 (IC_{50}= 251.67 µg/mL) while J1 AMCE was the most potent in killing MDA-MB-231 (IC_{50}= 347.67.67 µg/mL) cancer cells. Further downward assays were performed with the most potent leaf aqueous extract (B1 AMCE; dosage: 251.67 µg/mL) on 4T1 breast cancer cell line only to investigate its anti-cancer effect as it has a close resemblance of the advanced human breast cancer (stage IV); a cancer stage that patient has little chance of survival. B1 AMCE has a little effect (IC_{50}= 1000 µg/mL) on the normal breast cell line, MCF-10A rendering its safe profile. The

selected B1 AMCE managed to induce apoptosis in 4T1 cells as observed in the Annexin V/FITC and AO/PI assays as well as to arrest the cell cycle of 4T1 and induced the cells into sub G0/G1 stage. Metastasis of cancer cells is one of the hurdles needed to be curbed as it is the main factor leading to failure in cancer treatment. The anti-metastatic potential of B1 AMCE can be seen by the decreased percentage of migrated (31%) and invaded (44%) 4T1 cells in migration and invasion assays respectively. With the convincing results provided by the in vitro studies, the anti-cancer effects of B1 AMCE upon 4T1 breast cancer cells were further studied in vivo. The tumors harvested from 4T1 tumor-bearing mice showed a decrease in weight and volume from 1.45 g and 375 mm^3 in the untreated group to 1.2 g and 271.7 mm^3 in the B1 AMCE-treated group respectively. The H&E staining of sectioned tumor revealed a lower number of mitotic cells in the treatment group. B1 AMCE increased the circulation level of white blood cells and also regulated the immune system by increasing the population of helper and cytotoxic T-cells and natural killer cell population as well. The decreased level of angiogenesis-related protein and reduced number of metastasized 4T1 cell colonies to lung in the clonogenics assay exhibit the anti-metastatic potential of B1 AMCE on breast cancer and supported the in vitro studies. In addition, B1 AMCE treatment managed to reduce the oxidative stress caused by inflammation due to its antioxidant effect as evaluated by the nitric oxide and malondialdehyde assays. In conclusion, this study showed that the B1 AMCE is a promising candidate for cancer treatment especially in breast cancer and deserves further research as an alternative to conventional drugs while also stressed out the selection of *Annona muricata* sample which plays a significant role in determining its potential therapeutic effect on cancer.

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

PENGARUH *ANNONA MURICATA* LINN POLIMORFISME KE ATAS PENGHASILAN POLIFENOLIK DAN KESAN ANTI KANSER

Oleh

SYED UMAR FARUQ BIN SYED NAJMUDDIN

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Lazimnya, ubat-ubatan konvensional menghadapi kesukaran dalam memerangi kanser terutamanya disebabkan oleh rintangan terhadap rawatan dan kesan sampingan terhadap kesihatan, menyebabkan ramai telah beralih kepada tumbuhan ubatan sebagai kaedah alternatif rawatan. Komponen aktif dan sebatian yang terkandung dalam tumbuhan ubatan telah terbukti berkesan dalam merawat kanser pada peringkat in vitro dan in vivo manakala sebahagian daripada mereka telah diuji sehingga peringkat klinikal. Walaupun penemuan tersebut begitu meyakinkan, namun, terdapat satu aspek yang kerap terlepas pandang dan sebenarnya memerlukan perhatian yang sewajarnya. Sesuatu tumbuhan ubatan daripada spesies yang sama biasanya tidak mengandungi jumlah komponen aktif yang sama yang bertanggungjawab untuk melawan kanser. Tahap kandungan sebatian aktif mungkin berbeza bagi tumbuhan tersebut di lokasi berbeza. Dalam kajian ini, sebanyak 19 sampel *Annona muricata* Linn (durian belanda) dari lokasi yang berbeza (Negeri di Semenanjung Malaysia: Johor, Melaka, Negeri Sembilan, Selangor, Perak, dan Perlis) telah diuji untuk polimorfisme dan potensi yang dimiliki mereka dalam menentang kanser payudara. Melalui kaedah ISSR-PCR, sampel DNA menunjukkan kehadiran polimorfisme (72.41%) di kalangan sampel durian belanda dan disokong oleh perbezaan keputusan data dalam tahap antioksidan dan kajian anti- proliferatif menggunakan ekstrak daun pada sel kanser payudara (MCF -7, MDA -MB -231, dan 4T1). M1 mempunyai kandungan fenolik (73.2 µg/mL GAE) dan flavonoid (191.4 µg/mL CE) yang tertinggi dan juga mempuyai kemampuan antioksida tertinggi dalam analisis ORAC (254.7 µM) manakala A1 mengandungi kemampuan antioksida tertinggi dalam analisis FRAP. Berdasarkan profil IC_{50} daripada kajian anti-proliferatif, sampel B1 AMCE adalah yang paling poten dalam membunuh sel MCF-7 (IC_{50}= 221.67 µg/mL) dan sel 4T1 (IC_{50}= 251.67 µg/mL) manakala J1 AMCE merupakan sampel yang paling poten dalam membunuh sel kanser MDA-MB-231 (IC_{50}= 347.67.67 µg/mL). B1 AMCE menunjukkan kesan yang rendah (IC_{50}= 1000 µg/mL) terhadap sel payu dara normal, MCF-10A justeru membuktikan profilnya yang selamat untuk digunakan. Sampel B1 AMCE iaitu ekstrak akueus yang paling poten kesan tindakannya (dos: 251.67 µg/mL), telah dipilih untuk kajian anti-kanser yang

seterusnya ke atas sel payudara 4T1 sahaja kerana sel 4T1 menyerupai kanser payudara manusia tahap kritikal (tahap IV) dimana pesakit mempunyai peluang yang rendah untuk hidup. Sampel B1 AMCE yang dipilih telah berjaya mengarah apoptosis terhadap sel 4T1 melalui analisis Annexin V/FITC dan AO/PI serta mampu untuk menghentikan kitaran sel 4T1 dan menggalakkan kemasukan sel ke dalam peringkat sub G_0/G_1. Metastasis sel kanser adalah salah satu halangan yang perlu dibendung kerana ia adalah faktor utama yang membawa kepada kegagalan dalam rawatan kanser. Potensi anti-metastatik sampel B1 AMCE juga dapat dilihat melalui penurunan peratusan sel 4T1 yang migrasi (31%) dan invasi (44%) dalam analisis migrasi dan invasi sel 4T1. Dengan keputusan yang meyakinkan yang dicapai dalam kajian in vitro, kesan anti-kanser sampel B1 AMCE ke atas sel kanser payudara 4T1 telah dikaji lagi secara in vivo. Tumor yang diambil daripada mencit menunjukkan penurunan dari segi saiz dan berat daripada 1.45 g dan 375 mm^3 dalam kumpulan yang tidak dirawat kepada 1.2 g dan 271.7 mm^3 bagi kumpulan mencit yang dirawat dengan sampel B1 AMCE. Pewarnaan H&E pada tumor mendedahkan jumlah bilangan sel mitosis adalah lebih rendah bagi kumpulan yang dirawat dengan sampel B1 AMCE. B1 AMCE meningkatkan aras peredaran sel-sel darah putih dan juga mengawalatur sistem imun dengan meningkatkan sel T penolong dan sitotoksik dan populasi sel pembunuh semulajadi. Tahap penurunan ekspresi protein yang berkaitan dengan angiogenesis dan jumlah sel 4T1 yang metastasis ke paru-paru yang berkurang melalui kajian klonogenik menunjukkan potensi sampel B1 AMCE sebagai anti-metastatik terhadap kanser payudara seperti yang telah dibuktikan pada peringkat in vitro. Di samping itu, sampel B1 AMCE mampu mengurangkan tekana oksidasi akibat daripada keradangan melalui tindakan antioksidan sampel B1 AMCE sepertimana ditunjukkan oleh kajian nitrik oksida dan kajian malondialdehid. Kesimpulannya, kajian ini menunjukkan bahawa sampel B1 AMCE adalah calon yang berpotensi untuk merawat kanser terutamanya kanser payudara dan penyelidikan yang lebih mendalam amat diperlukan sebagai langkah alternatif kepada ubat-ubatan konvensional. Di samping itu, kajian ini menekankan bahawa pemilihan sampel durian belanda memainkan peranan penting dalam menentukan potensi terapeutik ke atas kanser.

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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

AAPH	2,2'-Azobis (2-amidinopropane) dihydrochloride
ACG	Acetogenin
AMCE	*Annona muricata* crude extract
ATP	Adenosine triphosphate
bp	Base pair
BSA	Bovine serum albumin
CO_2	Carbon dioxide
DMEM	Dulbecco's modified essential medium
ddH_2O	deionized distilled water
DMSO	Dimethyl sulfoxide
DNA	deoxyribonucleic acid
dNTPs	Dideoxynucleotide triphosphates (dATP, dTTP, dCTP, and dGTP)
EDTA	Ethylenediaminetetraacetic acid
ELISA	Enzyme Linked Immunosorbent Assay
EMT	Epithelial mesenchymal transition
et al.	et alii
EtBr	Ethidium Bromide
FADD	Fas-associated death domain
FBS	Fetal bovine serum
FC reagent	Folin Ciocalteu reagent
$FeSO_4$	Ferum sulphate
FITC	Fluorescin isothiocyanate
FRAP	Ferric Reducing Ability of Plasma
g	Gram
GA	Gallic acid

h	Hour(s)
ISSR	Inter-simple sequence repeat
Kb	kilo base
MDA	Malondialdehyde
mg	milligram
min	minute
ml	millilitre
mM	micro Molar
$MgCl_2$	Magnesium chloride
MTT	3-(4,-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide
Ng	nanogram
NH_4Cl	Ammonium chloride
NK	Natural killer cells
ORAC	Oxygen Radical Absorbance Capacity
PBS	Phosphate buffered saline
PCR	Polymerase chain reaction
PI	Propidium iodide
PS	Phosphatidylserine
RIPA	Radioimmunoprecipitation Assay buffer
RNA	Ribonucleic acid
rpm	Revoultion per minute
RPMI	Roswell Park Memorial Institute media
RT	Room temperature
s.c.	Subcutaneous
SDS	Sodium Dodecyl Sulfate
Taq	Thermus aquaticus thermostable DNA
TBA	Thiobarbituric acid

TBE	Tris Borate EDTA buffer
TCA	Trichloroacetic acid
TNF	Tumor necrosis factor
TPTZ	2, 4, 6-Tripyridyl-s-Triazine
UV	Ultraviolet
VEGF	Vascular endothelial growth factor
μL	microliter
%	Percentage

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CHAPTER 1

INTRODUCTION

Cancer is one of the diseases that still have no effective cure or treatment available yet. Surgery is practically performed as the first option recommended as cancer treatment to remove the entire tumor and surrounding tissue but this approach is not always significantly successful. The radical treatment may be useful in certain tumor cases like benign (non-cancerous) tumors but not possibly in malignant tumors which still has a high chance of cancer recurrence (Nguyen et al., 2008). Normally, in some patients, metastatic tumors invade and damage the local surrounding tissues when the patients were first diagnosed to have cancer (Seyfried & Huysentruyt, 2013). With the complex cascade of cancer nature, it is even worse and impossible to be able to treat patients in the given situation.

Furthermore, it is a necessary for patients to comply with all the medications, pre- and post-surgery. Of note, the chemotherapy drugs given are designed to target the tumor or the key molecules in the associated stromal microenvironment such as the antibodies and cytokines (Johnson & Brown, 2010). For instance, Bcr-Abl tyrosine kinase inhibitor is used to treat patient with chronic myeloid leukemia (CML) by inhibiting the growth of these leukaemia cells and induces apoptosis (An et al., 2010). However, this would not resolve the problem as other factors that might contribute to tumor's growth still active. Additionally, the chemotherapy drugs would also cause adverse effects towards patients (Lorizio et al., 2012) which results in the discontinuation of treatment by patients thus condemns the desired expectations of chemotherapy drugs.

These disappointing situations have led to the alternative way which involves the use of the medicinal plant. Medicinal plants are blessed with multiple nutrients, a wide spectrum of secondary metabolites, and also rich with antioxidants that proved beneficial in fighting cancer. For instance, curcumin which is derived from the spice turmeric has been shown previously to have the anti-oxidant, anti-inflammatory, anti-proliferative, and anti-angiogenic properties towards various tumor cell lines plus, it has an excellent safety profiles and only causes minimal adverse effects (Wang & Jiang, 2012). The aforementioned therapeutic properties outline the multiple-pronged action possessed by curcumin in targeting tumor cells and give the edge over chemotherapy drugs.

Annona muricata Linn has been shown in previous studies to have abundance of chemical compounds and secondary metabolites such as acetogenins, which are clinically proved in fighting cancer (Luna et al., 2006; Ragasa et al., 2012). This terrestrial plant which is also known by different names such as Graviola, Soursop or Guanabana has been used in many cultures as traditional remedies for a wide range of illness and disease including headaches, insomnia, and rheumatism (Hamizah et al., 2012). Despite the therapeutic values held by this medicinal plant, one major aspect

regarding the influence of polymorphism/genetic variation on the production of secondary metabolites has been overlooked. The production of secondary metabolites is actually a response by plants to cope with the harsh or ever changing environments. Guo et al. (2013) has reported that plant of similar species collected from different locations contain different level of secondary metabolites among them. Therefore, it would be essential to evaluate the polymorphism of *Annona muricata* Linn from different locations and its influence on polyphenolic compounds production and potency in treating breast cancer.

The main objective of this study is to set forth the anti-cancer potential of the natural product *Annona muricata* Linn that could act as an anti-tumorigenic and anti-metastasis, anti-angiogenesis, and anti-inflammatory agent as well as regulating the immune system. For instance, the anti-tumorigenic agent would be expected to have the negative effect towards the growth of cancerous cells and simultaneously bring them into apoptotic state while the anti-metastasis agent would inhibit the cells from migrating and invading into new area. It is also expected that there would be a variation among the *Annona muricata* Linn samples from the DNA polymorphism test and could be linked to the difference in level of antioxidants and some secondary metabolites and also the cytotoxicity effect of their crude extract.

Therefore, the objectives of this study were:

1. To analyze the DNA polymorphism of 19 Annona muricata Linn samples using ISSR marker
2. To evaluate the antioxidant level, cytotoxicity, and anti-metastatic effect of each sample of *Annona muricata* Linn in vitro
3. To evaluate the degree of cytotoxicity, anti-metastasis, anti-angiogenesis, regulation of immune system, and anti-inflammatory effects of *Annona muricata* Linn crude extract in vivo

The hypotheses of this study were: 1) DNA polymorphism of *Annona muricata* Linn occurs due to geographical factor/location; 2) crude extract of different *Annona muricata* Linn samples have different antioxidant level and cytotoxicity effect; and 3) the use of *Annona muricata* Linn extract as a mean to treat cancer is effective in terms of apoptosis induction, metastasis inhibition, anti-inflammatory, and immune regulation in vitro and in vivo model.

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