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ANTI-BREAST CANCER EFFECT AND MOLECULAR MECHANISM OF ACTION OF ARTONIN E USING In Silico, In Vitro AND In Vivo APPROACHES

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By

IMAOBONG CHRISTOPHER ETTI

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Faculty : Veterinary Medicine

In spite of advances in medicine, breast cancer still remains a leading cause of death among women worldwide. The resistance and high toxicity ensuing from available modern breast cancer treatment regimens have reduced the survival rate, causing most cancer patients to seek natural remedies with fewer side-effects as alternatives. This study was conducted to investigate the anti-breast cancer effect and elucidate the molecular mechanism of action of Artonin E, a prenylated flavonoid extracted from the stem bark of *Artocarpus elasticus*. The *in silico* anti-cancer effect of Artonin E was evaluated by targeting the human estrogen receptor α (hERα), present in approximately 70% of breast cancers. The Glide, Schrodinger Suite 2015 was used in the molecular docking study. The structure of the ligand binding domain of hERα was retrieved from Protein Data Bank while the structures of compounds were collected from PubChem database and prepared with the Schrodinger Suite. The compounds: Artonin E, Artobiloxanthone, Cycloartocarpesin, Artelastin, Artonin Y, Artonin U, Artonin L, Artonin T, Artonin S, Tamoxifen and the native ligand, were first examined for their drug-likeness before the conduct of the docking study. The cytotoxicity and mode of cell death induced by Artonin E on breast cancer cells were examined *in vitro* using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay, acridine orange (AO) and propidium iodide (PI) double staining, annexin V/FITC staining and DNA fragmentation analysis. Caspase-8 and -9 assays, total reactive oxygen species (ROS) assay, apoptosis- and cell cycle-related gene expression, human apoptosis proteome profiling array and Western blot analyses were used to determine the mechanism of apoptosis induced by Artonin E on MCF-7 and MDA-M-231 cells. The regulation of the breast cancer cell cycle was also investigated using flowcytometry. In the *in vivo* study, the mouse 4TI cell-induced mammary gland tumor model was used. The development of the tumor in mice was investigated over the 28 days of bi-weekly oral treatment with Artonin E. Serum biochemical parameters and liver, lung and kidney histopathology of treated mice were analysed. From the docking study, Artonin E had the best glide score among analogues of similar structure from the Artocarpus species and was chosen as a lead for further studies. Artonin E was shown to produce a half-

maximal growth inhibition in MCF-7 cells at concentrations of 6.9, 5.1 and 3.8 µM and in MDA-MB-231 at 14.3, 13.9 and 9.8 µM after 24, 48 and 72 hours of treatment, respectively. The greater cytotoxicity of Artonin E on MCF-7 when compared to MDA-MB-231 cells was confirmed by AO/PI and annexin V-FITC assays, thus, validating its strong binding affinity to the hERα, as shown by the molecular docking studies. Artonin E was less toxic to the normal breast epithelial (MCF 10A) cell line with IC_{50} of 45.80 µM. The morphological analysis and cell viability assay showed that the breast cancer cells treated with Artonin E lost viability and underwent apoptosis. Artonin E induced p53 independent G1 cell cycle arrest and apoptosis through ROS mediated mitochondrial pathway and livin suppression in MCF-7 breast cancer cells. It downregulated anti-apoptotic proteins with a corresponding upregulation of apoptosis inducers and caused a G2/M cell cycle arrest in MDA-MB 231 cells. These observations were evident by the gene expression analysis, caspase assay, ROS assays, apoptosis profiling and Western blot analysis. In the mouse mammary gland tumor model, Artonin E significantly ($p<0.05$) delayed tumor growth and reduced the relative tumor volume in a dose-dependent manner. By histopathological examination, the mammary gland tumor in mice treated with Artonin E showed lesser metastasis in a dose-dependent manner compared to the untreated control. Thus, this study showed that Artonin E has great potential to be developed as an anti-breast cancer agent.

Abstrak tesis yang dikemukakan kepda Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk Ijazah Doktor Falsafah

MEKANISME MOLEKUL KESAN ARTONIN E TERHADAP KANSER PAYUDARA YANG DITENTUKAN MELALUI PENDEKATAN *In Silico*, *In Vitro* AND *In Vivo*

Oleh

IMAOBONG CHRISTOPHER ETTI

November 2016

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Walaupun bidang perubatan kini sudah maju, namum kanser payudara masih kekal sebagai satu daripada penyebab utama kematian wanita di seluruh dunia. Kerentanan dan ketoksikan tinggi akibat daripada penggunaan regim rawatan moden terhadap kanser payudara telah mengurangkan kadar kemandirian, menyebabkan kebanyakan pesakit terpaksa mencari, sebagai ganti, cari rawatan semula jadi yang kurang kesan sampingannya. Kajian ini dijalankan untuk menyelidik mekanisma antikanser payudara Artonin E, suatu flavonoid terprenil yang diestrak daripada kulit batang pokok *Artocarpus elasticus*. Kesan antikanser *in silico* Artonin E dinilai dengan menyasarkan reseptor estrogen α manusia (hERα), yang wujud dalam lebih kurang 70% daripada kanser payudara. Glide, Schrodinger Suite 2015 telah diguna dalam kajian pengedokan molekul. Struktur domain pengikatan ligand pada hERα diperolehi daripada Protein Bank Data. Struktur sebatian diperolehi daripada pangkalan data PubChem dan disedia menggunakan Schrodinger Suite. Sebatian: Artonin E, Y, U, L, T, dan S, Artobiloksanton, Sikloartokarpesin, Artelastin, Tamoksifen dan ligand asli, terlebih dahulu diperiksa keserupaan drugnya sebelum menjalani kajian pengedokan. Kesitoksikan dan mod kematian sel yang diaruh oleh Artonin E terhadap sel kanser payudara dikaji secara *in vitro* dengan menggunakan assai 3-(4,5-dimetiltiazol-2-il)-2,5-difeniltetrazolium bromida (MTT), pewarnaan berganda akridina jingga (AO) and propidium iodida (PI), pewarnaan aneksin V-FITC, dan analisis pemfragmenan DNA. Assai kaspase-8 dan -9 dan spesies oksigen reaktif (ROS) sepenuh, apoptosis dan penyataan gen terkait kitaran sel, profil tatasusunan proteom apoptosis manusia, dan analisis pemendapan Western diguna untuk menentukan mekanisma apoptosis teraruh Artonin E terhadap sel MCF-7 dan MDA-MB-231. Pengawalaturan kitaran sel kanser payudara juga diselidiki mengguna sitometri aliran. Dalam kajian *in vivo* pula, model tumor kelenjar mama mencit teraruh sel 4T1 telah diguna. Perkembangan tumor diselidik dalam mencit terperlaku dua kali seminggu dengan Artonin E pada tempoh 28 hari. Parameter biokimia serum dan histopatologi hati, paru-paru, dan ginjal mencit terawatt dianalisis. Daripada kajian pengedokan, Artonin E menunjukkan skor glide terbaik dikalangan analog berstruktur serupa dengannya yang diperolehi daripada

spesies *Artocarpus* dan dipilih untuk kajian seterusnya. Artonin E telah menghasilkan kadar perencatan pertumbuhan separa maksimum pada kepekatan 6.9, 5.1, dan 3.8 μM untuk sel MCF-7 dan 14.3, 13.9 dan 9.8 μM untuk sel MDA-MB-231, masing-masing selepas 24, 48, dan 72 jam perlakuan. Ketoksikan Artonin E yang lebih tinggi terhadap sel MCF-7 daripada sel MDA-MB-231 telah disahkan melalui assai AO/PI dan aneksin V-FITC dan keafinannya yang tinggi terhadap rERα, seperti yang ditunjukkan melalui kajian pengedokan molekul. Artonin E kurang toksik terhadap jujukan sel (MCF 10A) epitelium payudara normal dengan IC_{50} 45.80 μM. Analisis morfologi dan asai kebolehhidupan menunjukkan yang sel kanser payudara terperlaku Artonin E hilang daya hidupnya dan mengalami apoptosis. Artonin E menyebabkan apoptosis pada sel MCF-7 melalui arah laluan intrinsik manakala pada sel MDA-MB-231 melalui kedua-duanya arah intrinsik dan ekstrinsik. Penemuan ini adalah jelas melalui analisis penyataan gen, assai kaspase dan ROS, dan pemprofilan apoptosis. Artonin E mengaruh penahanan G_0/G_1 pada kitaran sel MCF-7 dan hentian G_2/M pada kitaran sel MDA-MB-231. Dalam model tumor kelanjar mama mencit, Artonin secara ($p<0.05$) tererti melambatkan pertumbuhan dan mengurangkan isipadu tumor secara bersandarkan dos. Melalui pemeriksaan histopatologi, tumor kelenjar mama mencit yang diperlakukan Artonin E, berbanding kawalan tanpa rawatan, kurang kecenderungannya untuk metastasis secara bersandarkan dos. Dengan demikian, kajian ini menunjukkan yang Artonin E mempunyai potensi tinggi untuk dikembangkan sebagai agen antikanser payudara.

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"*Better is the end of a thing than the beginning thereof*" ~Ecclesiastes 7:8 (KJV)~

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

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Declaration by Members of Supervisory Committee

This is to confirm that:

- the research conducted and the writing of this thesis was under our supervision;
- supervision responsibilities as stated in the Universiti Putra Malaysia (Graduate Studies) Rules 2003 (Revision 2012-2013) were adhered to.

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LIST OF ABBREVIATIONS

hERα	Human estrogen receptor
ADMET	Absorption, distribution, metabolism and excretion
SDF	Structure-data file
cASTp	Computed Atlas of Surface Topography of proteins
PDB	Protein data bank
LBD	Ligand binding bank
SMAC/ Diablo	Second mitochondria-derived activator of caspases / direct IAP binding protein
TNF	Tumor necrosis factor
TRAIL	Tumor necrosis factor-related apoptosis inducing ligand
HO1/HMOX1/ HSP 32	Heme oxygenase decyclig 1
cIAP-1 & Ciap-2	Cellular inhibitors of apoptosis 1 and 2
IC_{50}	Half-maximal inhibitory concentration
ICAM-1	intercellular Adhesion Molecule 1
xIAP	x-linked inhibitor of apoptosis
S.I	Selectivity index

CHAPTER 1

INTRODUCTION

1.1 Overview

Breast cancer is a complex and heterogeneous disease, constituting an enormous burden to the world at large with increasing mortality rates. It is the most frequently diagnosed cancer and unfortunately the leading cause of cancer death among women (Coughlin and Ekweme, 2009) with an estimated 1.67 million new cases diagnosed in the year 2012 (Ferlay *et al*., 2013). Breast cancer can either be non-invasive, invasive, recurrent or metastatic, with the most common type, constituting approximately 80% of all breast cancers, being the invasive ductal carcinoma (IDC). The development of molecular profiling, has classified breast cancers into five subtypes: luminal A, luminal B, HER2, basal-like and normal-like breast cancers (Perou *et al*., 2000) with each subtype having a different prognosis and treatment response. The luminal types are estrogen receptor-positive with two subtypes, which are human estrogen receptor α and β with the former being implicated in approximately 70% of all breast cancer cases (Berger *et al*., 2012).

Epidemiologic studies have outlined both genetic and non-genetic factors that contribute to the development and progression of breast cancer at all stages. Only between 5 to 10% of breast cancer cases are hereditary. Between 90 to 95% of breast cancer cases are attributed to environmental factors (Easton *et al*., 1993; Anand *et al*., 2008) including age (at menarche, menopause and first pregnancy) (McPherson *et al*., 2000), diet, smoking, and alcohol consumption, (Lin *et al*., 2005), lack of physical activity (Elliassen *et al*., 2006) and the use of oral contraceptives (Althuis, 2003).

Breast cancer survivality is generally lower and resistance to drug therapy is a very common occurrence. The conventional therapeutic strategies in breast cancers include surgery, radiation and chemotherapy (Saxena *et al*., 2012). Due to their limited effectiveness and alarming side effects, there is still a pressing need for the development of alternative anti-breast cancer drugs, especially from natural products that are relatively safe and cheaply available. More than 50% of anticancer drugs approved by the United States Food and Drug Administration have been reported to stem from natural sources (Newman and Cragg, 2016; Dholwani *et al*., 2008).

Artonin E, 5-hydroxy-8,8-dimethyl-3-(3-methylbut-2-enyl)-2-(2,4,5-trihydroxyphenyl) pyrano [2,3-h] chromen-4-one is a prenylated flavonoid compound isolated from the stem bark of *Artocarpus elasticus*, (Rahman *et al*., 2016). The compound has been shown to possess a wide spectrum of *in vitro* biological activities such as antibacterial (Zajmi *et al*., 2015), antimicrobial (Kuete *et al*., 2011), anti-tumor (Rahman *et al*., 2016; Wongpankam *et al*., 2012), anti-migration and anti-invasion (Plaibua *et al*., 2013), antimalarial (Mustapha *et al*., 2010), and other medicinal properties (Suhartati *et al*., 2008: Oonphong *et al*., 2007). However, Artonin E has not been evaluated for its drug-likeness, its molecular interaction with the human estrogen receptor α in breast cancer

cells and the mechanism underlying the anti-breast cancer effect of Artonin E has not yet been reported.

Several approaches and models can be used in the investigation of the anti-breast cancer effect of a compound. Today, with the advancement in computational techniques, *in silico* models can be used to predict the drug-likeness of a promising compound as well as its effect on a target before the conduct of preclinical studies. This study is aimed at the determination of the molecular mechanism of the anti-breast cancer effect of Artonin E utilizing the *in silico*, *in vitro* and *in vivo* approaches.

1.2 Hypothesis

1. Artonin E will have a strong binding affinity to the human estrogen receptor α.
2. Artonin E will effectively inhibit the proliferation of breast cancer cell lines by causing cell death and cell cycle arrest
3. Artonin E will effectively inhibit mice mammary gland tumor growth *in vivo*

1.3 Objectives

The objectives of this study were to determine the:

1. *in silico* pharmacokinetic profile and molecular docking interaction of Artonin E and structural analogues on the human estrogen receptor α.
2. effect of Artonin E on the growth and mode of death of MCF 7 and MDA-MB 231 breast cancer cell lines.
3. regulation of the breast cancer cell cycle and the anticancer mechanisms of cell death induced by Artonin E via gene expression, apoptosis proteome profiling and Western blotting.
4. *in vivo* anticancer activity of Artonin E in a 4T1- mammary gland cancer line-induced mice model.

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