PHYTOCHEMICAL, *IN VITRO* AND *IN SILICO* ANALYSES OF HEXANIC *Alpinia galanga* EXTRACT IN CANCER CHEMO-PREVENTION STUDY ON BREAST CANCER CELLS

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DEDICATION

ALHAMDULILLAH

Every challenging work needs efforts as well as guidance of elders especially those who were very close to our heart.
My humble effort, I dedicate to my sweet and loving

My late Father
For earning an honest living for us and for supporting and encouraging me to believe in myself

& My Mother
A strong and gentle soul who taught me to trust Allah, affection, love, encouragement and prays of day and night make me able to get such success and honour

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ABSTRACT

Cancer is one of the major health concerns and leading causes of mortality worldwide. The major problem in the cancer chemotherapy is the drug-resistant of the established drugs. Therefore, the immediate search for anti-cancer agents from plant sources has been done intensively. The purpose of this study was to evaluate the anticancer effects of *Alpinia galanga* extracts against several breast cancer cell lines. The crude extracts were isolated via aqueous and different polarity of solvents such as hexane, acetone and ethanol using soxhlet extraction rotary evaporator. Cytotoxicity of crude extracts were screened by using MTT assay against normal human liver (WRL-68), and MCF-7, MDA-MB-231 and MDA-MB-468 breast cancer cell lines. Active crude extract with lowest IC_{50} value was selected for fractionated via column chromatography (CC) technique. Then, fractionates were re-evaluated for cytotoxicity profile and anti-migration activity. Further determination of active fraction induced cells death through cell cycle, apoptosis and pyroptosis was conducted flow cytometry and caspases bioluminescence studies. Their morphology structures were assessed under phase-contrast microscopy and inverted fluorescent-microscopy. Besides that, identification of bioactive molecules using gas chromatography-mass spectrophotometry (GC-MS) and prediction potential mechanism pathways was conducted through *in silico* molecular docking study. Active hexanic *A. galanga* extract with lowest IC_{50} value at 2.12 µg/mL and highest selectivity index (10.17) against MDA-MB-231 cells was fractionated. It was revealed that fraction F6-4 possessed potent anticancer and anti-migration activities. Interestingly, fraction F6-4 demonstrated both apoptosis and pyroptosis-induce cells death which involves ATP-dependent in MDA-MB-231 cells. The inhibition of MDA-MB-231 cells was characterized with apoptosis cells positive Annexin-V FITC due to exposure of phosphatidylserines (PS) on cell membrane after treatment and underwent cell cycle arrest at G_0/G_1 checkpoint. Further, the molecular mechanisms of inhibition of MDA-MB-231 cells by fraction F6-4 emphasizes on activation extrinsic and intrinsic caspases cascade, including inflammation caspase-1 (pyroptosis). Also, distinctly apoptosis and pyroptosis morphological changes were observed. Concomitantly, major bioactive compound was identified in both hexanic *A. galanga* and fraction F6-4 is 4-Chromanol. *In silico* molecular docking elucidated that 4-Chromanol induced apoptosis mechanisms through interaction between molecular extrinsic and intrinsic pathways, and also reveals as strong competitive inhibitor against Cdk2 and Cdk6. In conclusion, 4-Chromanol exhibited potent anticancer against triple negative breast cancer (TNBC) subtype and elucidate possible underlying mechanism(s) of apoptosis pathways.

ABSTRAK

Kanser adalah salah satu masalah utama kesihatan dan penyebab terbesar kematian di seluruh dunia. Masalah utama dalam kemoterapi kanser adalah ketahanan ubat-ubatan yang sedia ada. Oleh itu, pencarian segera agen-agen antikanser dari sumber-sumber tumbuhan telah diselidiki secara intensif. Tujuan kajian ini adalah untuk menilai kesan antikanser dari ekstrak *Alpinia galanga* terhadap beberapa jujukan sel-sel barah payudara. Ekstrak kasar telah dipencilkan menggunakan air dan pelarut yang mempunyai polariti yang berbeza seperti heksan, aseton dan etanol dengan menggunakan penyejat rotasi soxhlet. Sitotoksiti ekstrak-ekstrak dilakukan dengan menggunakan ujian MTT terhadap hati manusia normal (WRL-68), dan MCF-7, MDA-MB-231 dan sel-sel kanser payudara MDA-MB-468. Ekstrak aktif dengan nilai IC_{50} yang terendah dipilih untuk difraksinasi melalui teknik lajur kromatografi (CC). Kemudian, fraksi dinilai semula untuk sitotoksiti dan aktiviti anti-migrasi. Penentuan lebih lanjut bagi fraksi aktif mendorong kematian sel-sel melalui kitaran sel, apoptosis dan piroptosis dengan menggunakan kajian aliran sitometri dan bioluminesen caspase-caspase. Struktur morfologi sel-sel ini telah diperhatikan melalui kaedah mikroskopi fasa-kontras dan mikroskopi pendarfluor terbalik. Selain itu, pengenalpastian molekul bioaktif menggunakan kromatografi gas-spektrofotometri jisim (GC-MS) dan ramalan bagi potensi mekanisme dilakukan dengan kajian *in silico* pengendalian molekul. Ekstrak *A. galanga* heksan aktif dengan nilai IC_{50} terendah pada 2.12 µg/mL dan indeks selektiviti tertinggi (10.17) terhadap sel MDA-MB-231 telah difraksinasi. Ia mendedahkan bahawa fraksi F6-4 mempunyai aktiviti antikanser dan anti-migrasi yang kuat. Menariknya, fraksi F6-4 menunjukkan kematian sel terdorong oleh kedua-dua apoptosis dan piroptosis yang melibatkan kebergantungan ATP dalam MDA-MB-231 sel. Perencatan MDA-MB-231 sel dicirikan dengan sel apoptosis positif Annexin-V FITC kerana pendedahan fosfatidilserin (PS) pada membran sel selepas rawatan dan menjalani kitaran sel di pemeriksaan G_0/G_1 atau peralihan G_1/S. Selain itu, mekanisme molekul perencatan MDA-MB-231 sel oleh fraksi F6-4 menekankan pada pengaktifan ekstrinsik dan intrinsik litar caspase, termasuk keradangan caspase-1 (piroptosis). Juga, perubahan morfologi apoptosis dan piroptosis jelas diperhatikan. Serentak dengan itu, sebatian bioaktif utama dikenal pasti dalam kedua-dua heksan *A. galanga* dan fraksi F6-4 adalah 4-Chromanol. *In silico* pengendalian molekul menjelaskan bahawa 4-Chromanol mendorong mekanisme apoptosis melalui interaksi antara laluan molekul ekstrinsik dan intrinsik, dan juga menyatakan sebagai perencat daya saing yang kuat terhadap Cdk2 dan Cdk6. Kesimpulannya, 4-Chromanol mempamerkan antikanser yang kuat terhadap subjenis kanser payudara tiga negatif (TNBC) dan menjelaskan kemungkinan jaringan mekanisme apoptosis.

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4CM	-	4-Chromanol
abs	-	absorbance
ADME	-	Absorption, Distribution, Metabolism and Excretion
ADR	-	Adriamycin
AGA	-	*A. galanga* acetonic crude extract
AGH	-	*A. galanga* hexanic crude extract
AGE	-	*A. galanga* ethanolic crude extract
AGQ	-	*A. galanga* aqueous crude extract
ALT	-	Alanine aminotransferase
ATM	-	Ataxia-Telangiectasia Mutated
ATP	-	Adenosine triphosphate
ATR	-	Ataxia-Telangiectasia and Radis-related
BBB	-	Blood-Brain Barrier
BER	-	Base excision repair
BMP4	-	Bone morphogenetic protein
BRC	-	Breast Cancer
BSA	-	Bovine Serum Albumin
CAD	-	Caspase-activated DNase
CDK	-	Cyclin-dependent kinase
CFSE	-	CFDA-SE [5-(and 6)-carboxyfluorescein diacetate, succinimidyl ester]
CKIs	-	Cyclin dependent inhibitors
CNS	-	Central nervous system
CTD	-	C-terminal regulatory domain (CTD)
Cyt c	-	Cytochrome C
DAPI	-	4′,6-diamidino-2-phenylindole
DBD	-	Deoxyribonucleic acid (DNA)-binding domain
DBD	-	DNA binding core domain
DDR	-	DNA damage response
DISC	-	Death-inducing signaling complex

DMSO	-	Dimethyl sulfoxide
DPPH	-	2,2-diphenyl-1-picrylhydrazyl
D-PBS	-	Dulbecco-phosphate buffer saline
DRs	-	Death receptors
DSBs	-	Double-stranded breaks
EDTA	-	Ethylenediaminetetraacetic acid
ER	-	Estrogen receptor
EREs	-	Estrogen response elements
EGFR	-	Epidermal Growth Factor Receptor
F	-	fraction
FADD	-	FAS associated death-domain
FBS	-	Fetal Bovine Serum
FDA	-	Food and Drug Administration
Fe^{2+}	-	Ferrous ion
Fe^{3+}	-	Ferric ion
$FeCl_3.6H_2O$	-	Ferric(III) chloride hexahydrate / Iron(III) chloride hexahydrate
$FeSO_4$	-	Iron(II) sulfate
$FeSO_4.7H_2O$	-	Ferrous sulfate heptahydrate / Iron(II) sulfate heptahydrate
FRAP	-	Ferric Reducing Antioxidant Power
g	-	gram
GAE	-	Gallic Acid Equivalent
GC-MS	-	Gas Chromatography-Mass Spectrophotometry
GI	-	Gastrointestinal
HER	-	Human Estrogen Receptor
HIA	-	Human intestinalabsorption
HMR	-	Homologous recombination repair
HR	-	Homologous recombination
IC_{50}	-	50% Inhibitory Concentration
IMS	-	Intermembrane space
K_{oct}	-	Octonal/water partition coefficient
K_p	-	Permeability coefficient
L	-	Litre

LAR	-	Luminal androgen receptor
Log $P_{o/w}$	-	Partition coeffient between n-octanol and water
LOH	-	Loss of heterozygosity
Lum	-	Luminal
µg	-	microgram
µL	-	microliter
µm	-	micrometer
MC_A	-	Absolute migration capability
MDR	-	Multidrug-resistance
mg	-	milligram
MBC	-	Metastatic Breast Cancer
MDM2	-	Mouse double minute 2
MGMT	-	Methyl-guanine methyl transferase
mL	-	milliliter
MMR	-	Mismatch repair
MNTD	-	Minimal-Non-Toxic Dose
MOMP	-	Mitochondrial Outer Membrane Permeabilization
MR	-	Molecular refractivity
mt	-	mutant
MTT	-	(3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, a tetrazole)
MW	-	Molecular Weight
NCCD	-	Nomenclature Committee on Cell Death
NER	-	Nucleotide excision repair
NHEJ	-	Non-homologous end joining
OD	-	Optical density
PAINS	-	PAN Assay Interference Compounds
PARP-1	-	Poly(ADP-ribose) polymerase 1
PBS	-	Phosphate Buffer Saline
PCD	-	Programmed Cell Death
PDB	-	Protein Data Bank
P-gp	-	Permeability glycoprotein
PI	-	Propidium Iodide

PR	-	Progesterone Receptor
pRb	-	Protein retinoblastoma
PRD	-	Proline-rich domain
PS	-	Phosphatidylserine
PSA	-	Polar surface area
PTMs	-	p53 post-translation modications
Q	-	Quadrant
QE	-	Quercetin Equivalent
Rb	-	retinoblastoma
RCD	-	Regulated cell death
RTKs	-	Receptor tyrosine kinases
SEM	-	Standard error means
SI	-	Selectivity Index
TADs	-	N-terminal transactivation domains
TD	-	Tetramerization domain
TFC	-	Total Flavonoids Content
TK	-	Tyrosine kinase
TKI	-	Tyrosine kinase inhibitor
TLS	-	Translesion DNA synthesis
TNBC	-	Triple negative breast cancer
TPC	-	Total Phenolic Content
TPSA	-	Topological polar surface area
TP53	-	p53 tumor suppressor protein
UV	-	ultraviolet
V	-	voltage
VEGF	-	Vascular endothelial growth factor
v/v	-	volume by volume
WHO	-	World Health Organization
wt	-	wild type
^{o}C	-	Degree centrigrade
%	-	Percentage
+	-	Positive
-	-	Negative

2D	-	Two-Dimensional
3D	-	Three-Dimesional

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CHAPTER 1

INTRODUCTION

1.1 Background of Study

For decades, cancer is a major burden of disease worldwide (Fitzmaurice, 2019). Cancer is categorized as second leading cause of death after heart diseases (Ritchie and Roser, 2020). GLOBOCAN 2018 database reported that there will be 18.1 million new cancer cases and 9.6 million cancer deaths in year 2018 (Bray *et al.*, 2018; Ferlay *et al*., 2019). Statically depicted that 11.6% of the total cases of lung cancer is most commonly diagnosed cancer and with 18.4% of the total cancer deaths, followed by incidence of 11.6% cases of female breast cancer, 7.1% of prostate cancer, and 6.1% of colorectal cancer (Bray *et al.*, 2018). Colorectal cancer displayed 9.2% cases of mortality after lung cancer and follows with 8.2% of stomach cancer and liver (Bray *et al.*, 2018). Frequent cancer death among male dominates by lung cancer, charted by prostate, colorectal, liver and stomach cancer (Bray *et al.*, 2018). As for female, the most commonly diagnosed cancer and leading cause of cancer death is breast cancer, after that colorectal, lung and cervical cancer (Bray *et al.*, 2018).

Breast cancer (BRC) is an invasive cancer in women worldwide, with an estimated global prevalence (5-year) is 6875 099 cases were diagnosed and 626 679 deaths in year 2018 (Ferlay *et al*., 2018). In Malaysia, BRC has a high prevalence malignant cancer among Malaysian women with risk proportionate at one in nineteen of all ethnic groups (Lee *et al*., 2019). Statistically, it has been recognized as the first rank incidence with estimation of 7593 number of new cases and second cancer deaths with 2894 cases were reported in the year of 2018 (Ferlay *et al*., 2018).

To date, it is reported that disease-free survival of breast cancer survivors have increased greatly over the last few decades due to scientific advancements

including advances in mammographic screening and developed surgical, radiation, and adjuvant therapies in the area of breast cancer exploration (Yip *et al.*, 2014; Falstie-Jensen *et al.*, 2019; Siegel *et al.*, 2019; Stuart-Harris *et al.*, 2019). However, it is applicable only for an early stage of diagnoses and is circumscribed to the primary organ (Ahmad, 2013). Besides that, relapse may happen after early treatment due to presence of cancer stem cells and development of aggressive phenotype of cancer cells (Phi *et al.*, 2018; Ayob and Ramasamy, 2018; De Angelis *et al.*, 2019). In which, aggressive cancer cells resulting 40% recurrent of BRC (Chang *et al.*, 2016; Li *et al.*, 2018; De Angelis *et al.*, 2019). BRC recurrence may take place in the ipsilateral breast or chest wall after surgery, regional lymph nodes as well as distant sites and organs (Holleczek *et al.*, 2019). There are several breast cancer subtypes that characterized such as estrogen receptor (ER), progesterone receptor (PR), human estrogen receptor 2 (HER2) and triple negative breast cancers (TNBCs) that lack of all of them (Kennecke *et al.*, 2010; Jin and Mu 2015; Wu *et al.*, 2016b). Different breast cancer types have different recurrence patterns. For example, higher risk of recurrence during the initial 5 years after diagnosis in ER-negative breast cancers compared to ER-positive breast cancers (Mahmood *et al.*, 2015; Liedtke *et al.*, 2015; Ribnikar *et al.*, 2015).

Furthermore, aggressive phenotype cancer cells and existence of cancer stems cells are highly metastatic and resistant to conventional therapies. Over 90% of these patients die of metastasis breast cancer (MBC), when cancer cells spreads from their tumours of origin systemically and colonize at distant organs such as lungs, bones, brain and liver (Ma *et al.*, 2015; Pulido *et al.*, 2017; Oehrlich *et al.*, 2017; Jin *et al.*, 2018). These metastasis lesions conquer vital organs and subsequently forming multiple foci that are severely limit the option of surgical intervention (Jin and Mu, 2015; Al-Mahmood *et al.*, 2018; Savard *et al.*, 2019) and evolving drug resistance to the currently available systematic therapies (Kam *et al.*, 2014; Liedtke and Kolberg, 2016; El Sayed *et al.*, 2019; Larsson *et al.*, 2019).

Due to challenging of metastatic or therapy resistance tumour, BRC-related research has become central focus among researcher in oncology studies for novel drug discovery due to its aggressive and invasive phenotype. Plants (herbs, spices,

vegetables and medicinal plants) are utilized as the alternate medicinal to treat many of diseases by virtue of their antioxidant actions (Inoue *et al.*, 2019; Mintah *et al.*, 2019). In addition, numerous experimental studies emphasize the importance of compounds derived from plants or secondary metabolites the use of have proven to contribute to health benefits. Pharmacological activities reported that the plant extracts possesses antioxidant activities (Kasote *et al.*, 2015; Labiad *et al.*, 2017), anti-viral (Todorov *et al.*, 2015; Ogbole *et al.*, 2018), anti-diabetic (Agnaniet *et al.*, 2016; Sekhon-Loodu and Rupasinghe, 2019), anti-microbial (Mostafa *et al.*, 2018; Manandhar *et al.*, 2019), anticancer (de Giffoni de Carvalho *et al.*, 2019; Promraksa *et al.*, 2019), anti-inflammatory (Ghasemian *et al.*, 2016; Oguntibeju, 2018), and anti-ulcer (Mohod and Bodhankar, 2013; Abebaw *et al.*, 2017) activities. Thus, the plant extracts are among the most attractive sources to develop new therapeutic drugs which for development of chemopreventive regimens against breast cancer.

1.2 Problem Statement of Research

There are several treatment of MBC consists of complete surgical removal of the primary tumour, radiation, hormonal therapy and chemotherapy or immunotherapy (Al-Mahmood *et al.*, 2018). Surgical excision still the gold standard for diagnosis and treatment for solid tumour BRC, which can increase the overall survival rate and leads to reduction of breast cancer mortality by preventing the potentially incapacitating complications such as medullary compression and pathologic fractures (Thomas *et al.*, 2016; Lu *et al.*, 2017; Xiong *et al.*, 2018). However, emergent evidence suggests that surgical manipulation of the tumour can influence several pathophysiological processes that might increase possibility for accelerated growth of micro metastatic and formation of new metastatic foci that promote postoperative metastatic spread and tumour recurrence (Tohme *et al.*, 2017; Alieva *et al.*, 2018; Siegel *et al.*, 2019).

Alongside, chemotherapy is performing after surgical or radiotherapy in order to prevent recurrence and metastases are successful against primary tumour lesion and its residue (Phi *et al.*, 2018; Putzer *et al.*, 2017). Although targeted

chemotherapeutic agents minimized adverse effects and facilitates clinical efficacy, the challenging drug-resistant issue has reduce the effects of chemotherapy, contributing failure of treatment and metastatic progression (Kam *et al.*, 2014; Chen and Zhang, 2015; Cardoso *et al.*, 2017).

At present, there are several drugs such as tamoxifen, laptinib, raloxifene, toremifene, trastuzumab, pertuzumab, T-DM1 and etc. were approved by the FDA and widely used to target breast cancer that effective in blocking several molecular pathways (Masoud and Pagés, 2017; Niu *et al.*, 2019). Unfortunately, unexpected mechanisms of resistance of breast cancer against drug-therapies have been reported. Such as, main drawback in trastuzumab with conjugated monoclonal antibody (T-DM1) therapy with emergence of serious cardiac side effects (Beauclair *et al.*, 2007). Laptinib is a dual EGFR/HER2 tyrosine kinase inhibitor that acts as an ATP competitor (Clavarezza *et al*., 2016). However, poor prognosis and aggressive phenotype of overexpression of the receptor tyrosine kinase AXL may be implicated and cause resistance in preclinical breast cancer studies (Formisano *et al.*, 2014).

On the other hand, triple negative cancers (TNBC) has no currently treatment available due to association with an unfavourable prognosis and exhibit an incomplete pathological response (Gluz *et al.*, 2009; Grunt and Mariani, 2013). Yet, TNBC could respond to agents like PARP-1 inhibitors and EGFR inhibition, which may have HER1 as a potential target. Also, the monoclonal antibody cetuximab combined with cisplatin chemotherapy has shown promising results in a Phase II study against TNBC (Higgins and Baselga, 2011).

Therefore identification of new target molecules in breast cancer is highly desirable. Nevertheless, there are urgency attentions to exploit alternative proliferative pathways which are not yet fully understood in breast cancer subtypes like TNBCs. Approximately 79.8% of natural products or compounds mimicked products in one form or another were reviewed by Newman and Cragg, 2016 as sources of new drugs over the 34 years from 1981 to 2014. Moreover, from the data presented, there are 17 out of the 246 of anticancer drugs approved by FDA (Newman and Cragg, 2016). A recent review by Butler *et al*., 2014 lists 133 natural

products and natural product analogues undergoing clinical trials or in registration at the end of 2013 and out of 71 of these compounds investigated as potential oncology treatments with 31 compounds in phase III clinical trial. Natural products could be naturally occurring in various plants, bacteria, fungi and marine sources. Predominantly, plants (herbs, spices, vegetables and medicinal plants) have been used as the basis of medicines for thousands of years and diverse culture around the world (Butler *et al*., 2014; Ngo *et al*., 2013). Henceforth, investigation on structurally diverse compounds in plant extracts can be a promising approach in drug discovery.

In this research, discover bioactive natural products from Malaysian plants used in folk medicine such as *Alpinia galanga* (L) as candidates for future clinical development against breast cancer will be conducted. Additionally, molecular and cellular biology as well as analytical chromatographic studies and molecular docking will be performed to elucidate the possible pathways that induce program cells death in breast cancer.

1.3 Objectives

To achieve this goal, the present study was organized to select safe and effective Malaysian plants with anticancer ability and determine its chemical constituents. The objectives were as follows:

1. To isolate crude polarity based extraction using aqueous and different solvents (hexane, acetone and ethanol) of *Alpinia galanga* (*A. galanga*) using soxhlet extraction rotary evaporator, and to evaluate phytochemical properties and quantify phenolic content, flavonoid content and antioxidant properties of isolated *A. galanga* crude extracts.

2. To investigate *in vitro* anticancer potential of isolated *A. galanga* crude extracts against breast cancer (MCF-7, MDA-MB-231, MDA-MB-468) by using the MTT assay.

3. To determine *in vitro* anticancer potential of isolated fractionates hexanic *A. galanga* rhizomes and anti-migration of fraction F6-4 against MDA-MB-231 cells.

4. To investigate the cell cycle, apoptosis and pyroptosis-inducing of isolated fraction F6-4 of hexanic *A. galanga* rhizomes against MDA-MB-231 cells and to identify the bioactive compounds via gas chromatography-mass spectrometry (GC-MS).

5. To elucidate molecular mechanism apoptosis pathways of major bioactive compound of isolated fraction F6-4 of hexanic *A. galanga* rhizomes (4-Chromanol) by using *in silico* molecular docking.

1.4 Scope of Research

The aims of this research were achieved with several outlines of limitations. On the basis of literature surveys for anti-proliferative investigation on rhizomes, *Alpinia galanga* (*A. galanga*) was selected in this study. Aqueous and different polarity solvents such as hexane, ethyl acetate and methanol were used to isolate crude extracts by using sohlex extraction and were freeze-dried to remove any residual of water. Four isolated crude extracts were preliminarily analysed for their phytochemicals such as terpenoids, tannins and coumarins. Also, quantifying for phenolic contents (TPC), total flavonoids (TFC) and antioxidant activities such as ferric reducing antioxidant power (FRAP) and scavenging of DPPH radicals.

Next, all isolated crude extracts were subjected against normal liver cells (WRL-68) in order to verify the cytotoxicity towards normal cells. On the other hand, there were two subtypes of breast cancer tested in this study. Such as MCF-7 cells line associated with ER, PR and HER2 receptor (HER2). Another subtype was triple negative breast cancers (TNBCs) that absence of all of them, namely MDA-MB-231 and MDA-MB-468 cell lines. Anti-proliferative effects were measured *in vitro* by using MTT ([3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide]) assays for 72 hours incubation. The IC_{50} values were generated via

GraphPad sigmoidal curve. The lowest IC_{50} value obtained of anti-proliferative on selective breast cancer cells was fractionated via column chromatography (CC). All fractionates were re-evaluated their anti-proliferative against breast cancer cells that sensitive toward isolated crude extract beforehand. Then, the most potent anticancer fraction was further evaluated for their ability acts as anti-migration agent.

The pro-apoptotic assay such as Annexin- V FITC and cell cycle-DNA on effective fraction was conducted via flow cytometry analysis. Moreover, bioluminescence studies including ATP and caspases were performed via ELISA microplate reader. Aside than initiator caspases (caspase-8 and -9) and effector caspases (caspase-3) to evaluate extrinsic and/or intrinsic pathways involve in apoptotic-induce cell death, inflammatory caspase-1 was utilized for detection of pyroptotic-induce cell death. Also, morphological changes of apoptotic-induce and pyroptotic-induce cell death were visualized using phase contrast inverted microscope and inverted fluorescence microscopy (Nikon). For fluorescence observation, treated cells were fixed by using 3.7% formaldehyde and triple staining of CFDA-SE [5-(and 6)-carboxyfl uorescein diacetate, succinimidyl ester], known as CFSE, 4',6-Diamidino-2-phenylindole (DAPI) and propidium iodide (PI) was performed.

The bioactive compound/(s) of effective fractionation that potentiated the anticancer effect of breast cancer was identified with gas chromatography-mass spectrometry (GC-MS). Finally, *in silico* methodologies such as molecular docking were implemented as alternative to assess potential drug candidates in non-clinical development and to ensure that valuable resources are apportioned to the most promising candidates. Thus, all the target proteins were extracted from PDB server, several online tools were exploited such as PatchDock and FireDock were utilized for molecular docking; Swiss ADME and Swiss Param were used for physicochemical analysis of bioactive compound/(s) and preparation ligand respectively. Interaction between ligand and proteins were conducted by using Proteins Plus server. A computational analysis was established in an attempt to predict the underlying mechanism(s) action of bioactive compound/(s) by using the pathway-specific molecular targets of extrinsic and intrinsic apoptotic pathways.

1.5 Significant of Research

The emergence of drug resistance to commonly available drug targeted therapy has been emerged as a major hurdle for metastatic or therapy resistance breast tumour. Therefore identification of new target molecules in breast cancer is highly desirable due to its aggressive and invasive phenotype. Also, there are urgency attentions to explore alternative proliferative pathways that not yet fully understood in breast cancer subtypes like triple negative breast cancer (TNBCs). In Malaysia, there were many medicinal plants were reported to exhibits potential anticancer activities. Hence, in this study, their phytochemicals were explored further. It was done to highlight the mechanisms and mode of anticancer actions based on *in vitro* and *in silico* analyses. The study could provide a significant finding of the anticancer potential, and explore their additional values as highly beneficial herbs.

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