



UNIVERSITI PUTRA MALAYSIA

***APOPTOSIS AND CELL CYCLE MECHANISMS OF AMPELOPSIN E ON
TRIPLE NEGATIVE BREAST CANCER CELLS***

NAPSIAH ABD RAHMAN

IB 2018 6



**APOPTOSIS AND CELL CYCLE MECHANISMS OF AMPELOPSIN E ON
TRIPLE NEGATIVE BREAST CANCER CELLS**

By

NAPSIAH ABD RAHMAN

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

December 2017

COPYRIGHT

All materials contained within the thesis, including without limitation text, logos, icons, photographs and all other artwork, are copyright materials of Universiti Putra Malaysia unless otherwise stated. Use may be made of any material contained within the thesis for non-commercial purposes from the copyright holder. Commercial use of material may only be made with the express, prior, written permission of Universiti Putra Malaysia.

Copyright © Universiti Putra Malaysia



Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfillment of the requirements for the degree of Master of Science

APOPTOSIS AND CELL CYCLE MECHANISMS OF AMPELOPSIN E ON TRIPLE NEGATIVE BREAST CANCER CELLS

By

NAPSIAH ABD RAHMAN

December 2017

Chairman : Latifah Saiful Yazan, PhD
Faculty : Institute of Bioscience

Cancer remains as the second leading cause of death after cardiovascular disease, worldwide. Approximately 14.1 million new cancer cases and 8.2 million cancer deaths were reported in 2012. Breast cancer is the most common cancer among women with 522,000 deaths in 2012 alone. There are a few treatment modalities for breast cancer that include chemotherapy, mastectomy, biological therapy and hormone replacement therapy. Chemotherapy remains as the main treatment, but it comes with severe side effects such as immunosuppression and formation of secondary tumor. Therefore, people now are turning to natural products that include the use of plant as an alternative for management of the cancer. Indeed, plants have been a good source of a few anticancer drugs such as taxol, vincristine and vinblastine. *Dryobalanops* or also known as Kapur can be found in tropical rain forest of West Malesia (Peninsular Malaysia, Borneo and Sumatra). There are only seven species of *Dryobalanops*, which are *D. rappa*, *D. aromatica*, *D. lanceolata*, *D. beccari*, *D. fusca*, *D. keithii* and *D. oblongifolia*. Resveratrol oligomer is a major group of bioactive compounds that can be found in *Dryobalanops* species was reported to exhibit antioxidant, antifungal, anti-HIV, anti-platelet aggregation, tyrosinase and cyclooxygenase I and II inhibitory properties. The objective of this study was to determine the cytotoxicity of resveratrol oligomers (ampelopsin E, ampelopsin F, flexuosol A, laevifonol, Malaysianol A, Malaysianol D and nepalensinol E) from *Dryobalanops species* towards non-hormone dependent (MDA-MB-231) and hormone dependent (MCF-7) breast cancer, human colorectal adenocarcinoma cancer (HT-29), alveolar carcinoma (A-549), cervical adenocarcinoma (HeLa), non-tumorigenic epithelial breast (MCF-10A) and mouse embryonic fibroblast (NIH/3T3) cells. The cytotoxicity was determined by MTT assay. The cells were treated with the compounds (0.94-30 μ M) for 72 hours. The mode of cell death was evaluated by using an inverted light microscope and annexin V/PI flow-cytometry analysis. Cell cycle analysis was performed by using a flow cytometer. Effects of ampelopsin E on the expression of NF- κ B, p53, p21, Cyclin A, Cyclin B1, CDK1, Bax and Bcl-2 were analysed by using Western blotting. Data showed that ampelopsin E was most cytotoxic towards MDA-MB-231 cells with the IC₅₀ (50% inhibition of cell viability compared to the control) of 14.5 $\pm$ 0.71 μ M. Cell shrinkage, membrane blebbing and formation apoptotic bodies characteristic of apoptosis were

observed following treatment with ampelopsin E. The annexin V/PI flow cytometric analysis further confirmed that ampelopsin E induced apoptosis in MDA-MB-231 cells. Cell cycle analysis revealed that ampelopsin E induced G₂/M phase cell cycle arrest in the cells. The expression level of Bax and p21 was significantly up-regulated ($p < 0.05$), whereas, the expression level of NF- κ B, p53, Cyclin A, Cyclin B1, CDK1 and Bcl-2 was significantly down-regulated ($p < 0.05$) after treatment with ampelopsin E. In conclusion, ampelopsin E induced apoptosis and cell cycle arrest in MDA-MB-231 cells. It is postulated that the induction of apoptosis is via NF- κ B p53/p21 and intrinsic pathways, and the G₂/M arrest is via p53-independent/p21 pathway. Therefore, ampelopsin E has the potential to be developed into an anticancer agent for the treatment of triple negative breast cancer.

Abstrak thesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan ijazah Master Sains

MEKANISMA APOPTOSIS DAN KITARAN SEL OLEH AMPELOPSIN E DI KANSER PAYUDARA *TRIPLE NEGATIVE*

Oleh

NAPSIAH ABD RAHMAN

Disember 2017

Pengerusi : Latifah Saiful Yazan, PhD
Fakulti : Institut Biosains

Kanser kekal sebagai punca kedua utama kematian selepas penyakit kardiovaskular di seluruh dunia. Kira-kira 14.1 juta kes baharu dan 8.2 juta kes kematian akibat kanser dilaporkan pada tahun 2012. Kanser payudara merupakan kanser yang paling kerap dikalangan wanita dengan 522,000 kes kematian pada 2012 sahaja. Terdapat beberapa kaedah rawatan untuk kanser payudara termasuklah kemoterapi, mastektomi, terapi biologi dan terapi penggantian hormon. Kemoterapi kekal sebagai rawatan utama, tetapi ia hadir dengan kesan sampingan yang teruk seperti penekanan sistem imun dan pembentukan tumor sekunder. Oleh itu, masyarakat kini beralih kepada produk semulajadi termasuklah penggunaan tumbuh-tumbuhan sebagai alternatif untuk pengurusan kanser. Hakikatnya, tumbuh-tumbuhan telah menjadi sumber utama bagi beberapa ubatan anti-kanser seperti taxol, vincristine dan vinblastine. *Dryobalanops* atau dikenali juga sebagai pokok Kapur boleh ditemui di dalam hutan hujan tropika Barat Malesia (Semenanjung Malaysia, Borneo dan Sumatera). Terdapat hanya tujuh spesis *Dryobalanops* iaitu *D. rappa*, *D. aromatica*, *D. lanceolata*, *D. beccari*, *D. fusca*, *D. keithii* dan *D. oblongifolia*. Resveratrol oligomer adalah kumpulan utama sebatian bioaktif yang boleh ditemui daripada spesis *Dryobalanops* yang dilaporkan mempamerkan ciri-ciri antioksidan, anti-kulat, anti-HIV, anti-pengumpulan platelet, *tyrosinase* dan *cyclooxygenase* I dan II. Objektif kajian ini adalah untuk menentukan kesitotoksikan resveratrol oligomer (ampelopsin E, ampelopsin F, flexuosol A, laevifonol, Malaysianol A, Malaysianol D dan nepalensinol E) daripada spesis *Dryobalanops* terhadap kanser payudara tidak bergantung kepada hormon (MDA-MB-231) dan bergantung kepada hormon (MCF-7), kanser kolorektal (HT-29), kanser paru-paru (A-549), kanser servik (HeLa), sel bukan kanser payudara (MCF-10A) dan fibroblas embrio tikus (NIH/3T3). Kesitotoksikan ditentukan oleh asai MTT dirawat dengan sebatian (0.94-30 μM) selama 72 jam. Cara kematian sel telah ditentukan dengan mikroskop cahaya keterbalikan dan analisis sitometri aliran dengan Annexin-V/PI. Analisis kitaran sel telah dilaksanakan dengan sitometri aliran. Kesan ampelopsin E terhadap pengekspresan NF- κB , p53, p21, Cyclin A, Cyclin B1, CDK1, Bax dan Bcl-2 telah dianalisis dengan menggunakan pembloatan Western. Data menunjukkan ampelopsin E paling sitotoksik terhadap sel MDA-MB-231 dengan IC_{50} (50% perencatan kemandirian sel berbanding kawalan) $14.5 \pm 0.71 \mu\text{M}$. Pengecutan sel,

pembengkakan membran dan pembentukan badan apoptotik telah diperhatikan berikutan rawatan dengan ampelopsin E. Analisis sitometri aliran dengan Annexin-V/PI mengesahkan bahawa ampelopsin E mengaruh apoptosis terhadap sel MDA-MB-231. Analisis kitaran sel pula mendedahkan bahawa ampelopsin E mengaruh perencatan kitaran sel di fasa G₂/M. Tahap ekspresi p21 dan Bax ditingkatkan secara ketara ($p < 0.05$), manakala, tahap ekspresi NF- κ B, p53, Cyclin A, Cyclin B1, CDK1 dan Bcl-2 diturunkan secara ketara ($p < 0.05$) selepas rawatan dengan ampelopsin E. Kesimpulannya, ampelopsin E mengaruh apoptosis dan merencat kitaran sel dalam sel MDA-MB-231. Ianya dicadangkan bahawa aruhan apoptosis adalah melalui laluan NF- κ B p53/p21 dan intrinsik, dan perencatan di fasa G₂/M adalah melalui laluan tidak bersandar p53/p21. Oleh itu, ampelopsin E mempunyai potensi untuk dibangunkan sebagai agen anti-kanser payudara tiga kali ganda negatif.



ACKNOWLEDGEMENT

Firstly, I would like to express my sincere gratitude to my supervisor, Assoc. Prof. Dr. Latifah Saiful Yazan, for her continuous support, patience, motivation and immense knowledge in completing this work hence the thesis. I could not imagine having a better advisor and mentor in my journey as a Master's student.

I also would like to extend my sincere gratitude to my co-supervisors, Assoc. Prof. Dr. Sharida Fakurazi and Assoc. Prof. Dr. Norizan Ahmat, for their support and valuable comments in making this research a success.

Not to be forgotten, my sincere thanks to Dr. Agustono Wibowo, Dr. Foo Jhi Biau, Dr. Tor Yin Sim, Dr. Yeap See Kwong, Ms. Ong Yong Sze, Mrs. Wan Nor Hafiza Wan Abd Ghani, Mr. Zainal Abidin Razali and Ms. Tan Woan Sean for their generosity to assist me throughout the study.

I am very grateful to all science officers, assistants and technicians in Institute of Bioscience, Universiti Putra Malaysia, Mrs. Norhaszalina Md Isa, Mrs. Norhafiza Azwa Ghozali, Mrs. Nancy Liew Woan Charn, Mrs. Nurul Wahida Abd. Rani, Mr. Mohammad Fareeq Zainol Abidin and Ms. Norsharina Ismail. Thank you very much for the guidance and kind assistance in handling the equipment and chemicals in the laboratories.

I would also like to acknowledge the financial support from the Ministry of Education Malaysia for the MyBrain15 (MyMaster) Scholarship, and Universiti Putra Malaysia for the Graduate Research Fellowship (GRF) Scholarship for my study.

Last but not the least, I would like to convey my utmost appreciation to my husband, Zainal Abidin Husin, for his spiritual and financial support. My gratitude also goes to my daughter (Irdina Safiya Zainal Abidin), mother (Faridah Othman), my late father (Abd Rahman Mohd Kassim), my brother (Aminur Rashid Abd Rahman), my younger sister (Siti Hajar Abd Rahman) and in-laws for their understanding.

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:

Latifah Saiful Yazan, PhD

Associate Professor
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Chairman)

Sharida Fakurazi, PhD

Associate Professor
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Member)

Norizan Ahmat, PhD

Associate Professor
Faculty of Applied Sciences
Universiti Teknologi MARA
(Member)

ROBIAH BINTI YUNUS, PhD

Professor and Dean
School of Graduate Studies
Universiti Putra Malaysia

Date:

Declaration by graduate student

I hereby confirm that:

- this thesis is my original work;
- quotations, illustrations and citations have been duly referenced;
- this thesis has not been submitted previously or concurrently for any other degree at any other institutions;
- intellectual property from the thesis and copyright of thesis are fully-owned by Universiti Putra Malaysia, as according to the Universiti Putra Malaysia (Research) Rules 2012;
- written permission must be obtained from supervisor and the office of Deputy Vice-Chancellor (Research and Innovation) before thesis is published (in the form of written, printed or in electronic form) including books, journals, modules, proceedings, popular writings, seminar papers, manuscripts, posters, reports, lecture notes, learning modules or any other materials as stated in the Universiti Putra Malaysia (Research) Rules 2012;
- there is no plagiarism or data falsification/fabrication in the thesis, and scholarly integrity is upheld as according to the Universiti Putra Malaysia (Graduate Studies) Rules 2003 (Revision 2012-2013) and the Universiti Putra Malaysia (Research) Rules 2012. The thesis has undergone plagiarism detection software.

Signature: _____ Date: _____

Name and Matric No.: Napsiah Abd Rahman (GS40346)

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) are adhered to.

Signature : _____

Name of Chairman of
Supervisory Committee : Assoc. Prof. Dr. Latifah Saiful Yazan

Signature : _____

Name of Member of
Supervisory Committee : Assoc. Prof. Dr. Sharida Fakurazi

Signature : _____

Name of Member of
Supervisory Committee : Assoc. Prof. Dr. Norizan Ahmat

TABLE OF CONTENTS

	Page
ABSTRACT	i
ABSTRAK	iii
ACKNOWLEDGEMENT	v
APPROVAL	vi
DECLARATION	vii
LIST OF TABLES	xii
LIST OF FIGURES	xiii
LIST OF APPENDICES	xv
LIST OF ABBREVIATIONS	xvi
 CHAPTER	
1 INTRODUCTION	1
1.1 Background	1
1.2 Objective	3
1.2.1 General Objective	3
1.2.2 Specific Objective	3
1.3 Hypothesis	4
 2 LITERATURE REVIEW	5
2.1 Cancer	5
2.1.1 Breast cancer	5
2.1.2 Treatments of breast cancer	6
2.2 Natural products as source of anticancer agents	7
2.2.1 <i>Dryobalanops</i>	7
2.3 Screening for antibreast cancer agents	13
2.4 Cell cycle and cancer	15
2.4.1 The role of p21 in cell cycle	17
2.4.2 The role of p53 in cell cycle	18
2.4.3 The role of NF- κ B in cell cycle	18
2.5 Cell death	
2.5.1 Apoptosis and cancer	19
2.5.2 Necrosis and cancer	22
2.6 Method used in distinguishing apoptosis from necrosis	23
 3 MATERIALS AND METHODS	26
3.1 Compounds	26
3.1.1 Preparation of test solution	26
3.2 Chemicals	26
3.3 Cell culture	27
3.4 Determination of cytotoxicity	29
3.5 Determination of morphological changes	29
3.6 Determination of cell cycle arrest	29
3.7 Determination of mode of cell death	30
3.8 Determination of level of protein expression by Western blotting	30
3.8.1 Protein extraction and separation	30

3.8.2	Protein quantification	31
3.8.3	Protein separation	31
3.8.4	Protein transfer	32
3.8.5	Antibody incubation	32
3.8.6	Protein detection	32
3.9	Statistical analysis	33
4	RESULTS	34
4.1	Cytotoxicity of the resveratrol oligomers (ampelopsin E, ampelopsin F, flexuosol A, laevifonol, Malaysianol A, Malaysianol D and nepalensinol E) towards MDA-MB-231, MCF-7, HT-29, A-549, HeLa, MCF-10A and 3T3 cells.	34
4.2	Morphological changes of MDA-MB-231 cells treated with ampelopsin E	36
4.3	Cell cycle arrest induced by ampelopsin E in MDA-MB-231 cells	39
4.4	Mode of cell death induced by ampelopsin E in MDA-MB-231 cells	41
4.5	Effects of ampelopsin E on the level of protein expression of MDA-MB-231 cells	44
5	DISCUSSION, CONCLUSION AND FUTURE WORKS	48
5.1	Discussion	48
5.2	Conclusion	54
5.3	Future works	54
	REFERENCES	55
	APPENDICES	76
	BIODATA OF STUDENT PUBLICATION	80
		81

LIST OF TABLES

Table		Page
2.1	The mass of resveratrol oligomers isolated from different species of <i>Dryobalanops</i> .	11
2.2	Differences in the features of apoptosis and necrosis	23
4.1	Cytotoxicity of the resveratrol oligomers isolated from <i>Dryobalanops</i> species towards cancer cell lines at 72 hours reflected by the IC ₅₀ values as determined by MTT assay	35

LIST OF FIGURES

Figure		Page
2.1(a)	Botanical illustration flowers, leaves and fruit sepals of <i>Dryobalanops sp</i>	8
2.1(b)	'Crown shyness' phenomenon of mature <i>Dryobalanops sp</i> tree	8
2.2	Chemical structures of <i>trans</i> - and <i>cis</i> -resveratrol	9
2.3	Classification of resveratrol oligomers	10
2.4	Chemical structure of some resveratrol oligomers isolated from <i>Dryobalanops</i> species	12
2.5	Mammalian cell cycle	15
2.6	The molecular pathway of p21 functions in controlling cell cycle	17
2.7	Events in apoptosis and necrosis	24
3.1	An overview of the study experiment	28
4.1	Morphological changes of ampelopsin E-treated MDA-MB-231 cells observed under an inverted light microscope	37
4.2	Close-up views of ampelopsin E-treated MDA-MB-231 cells	38
4.3(a)	Cell cycle profile of MDA-MB-231 cells treated with ampelopsin E at different time point	40
4.3(b)	Number of MDA-MB-231 cells treated with ampelopsin E in different phase of the cell cycle at different time point	41
4.4(a)	Number of viable, apoptotic and necrotic/secondary necrotic cells of ampelopsin E-treated MDA-MB-231 cells as determined by a flow cytometer at different time point	42
4.4(b)	The percentage of viable, early apoptotic and necrotic/secondary necrotic cells of untreated and ampelopsin E-treated MDA-MB-231 cells at different time point	43
4.5(a)	Expression level of NF- κ B, p53, p21, Cyclin A, Cyclin B1, CDK1, Bax, Bcl-2 and Bax/Bcl-2 ratio of ampelopsin	45

E-treated MDA-MB-231 cells as determined by Western blotting analysis

- | | | |
|--------|--|----|
| 4.5(b) | Relative fold change of the level of protein expression in ampelopsin E treated MDA-MB-231 cells at 24 hours which was normalised against beta-actin | 46 |
| 4.5(c) | Relative fold change of the level of protein expression in ampelopsin E treated MDA-MB-231 cells at 24 hours which was normalised against beta-actin | 47 |
| 5.1 | Proposed mechanism underlying the anticancer properties of ampelopsin E towards MDA-MB-231 cells | 53 |



LIST OF APPENDICES

Appendix		Page
A	Effects of ampelopsin E on the viability of MDA-MB-231 cells as determined by MTT assay	76
B	Effects of ampelopsin E on the viability of MCF-7 cells as determined by MTT assay	77
C	Effects of ampelopsin E on the viability of MCF-10A cells as determined by MTT assay	78
D	Effects of doxorubibin on MDA-MB-231 cells as determined by MTT assay	79

LIST OF ABBREVIATIONS

BRCA1	Breast cancer 1
CDK	Cyclin-dependent kinase
CHK	Checkpoint kinase
CKI	Cyclin-dependent kinase inhibitor
DR	Death Receptor
ER	Estrogen receptor
<i>E2F</i>	Genes encoding transcription factor
IKK	I κ B kinase
NF- κ B	Nuclear factor-kappa B
PMSF	Phenylmethanesulfonyl fluoride
PR	Progesterone receptor
PS	Phosphatidylserine
P21	Potent cyclin-dependent kinase inhibitor
P53	Tumour protein p53 (TP53)
RB	Retinoblastoma protein
TNBC	Triple negative breast cancer
TNF- α	Tumor necrosis factor- α
TRAIL	TNF-related apoptosis inducing ligand
TUNEL	Terminal deoxynucleotidyl transferase (TdT) dUTP Nick-End labeling assay

CHAPTER 1

INTRODUCTION

1.1 Background

There have been approximately 14.1 million cancer cases recorded worldwide in 2012 and 8.2 million were cancer-related deaths. Breast cancer is the second most commonly diagnosed cancer with 1.7 million cases (11.9%) after lung cancer with 1.8 million cases (13%). Approximately 522,000 cases of breast cancer deaths in females were reported, which 324,000 cases occurred in less developed regions and 198,000 cases in more developed regions (Ferlay et al., 2015).

Cancer is an uncontrolled growth of cells that results from genetic mutations and it can invade to other tissues. Breast cancer is a heterogeneous disease with several biological subtypes, which are normal-like, luminal A, luminal B, basal-like and HER2⁺ enriched (Glück, 2014). There are two factors that lead to development of breast cancer, which are external factors such as viruses, diet, radiations, chemicals and infectious organisms and internal factors such as hormones, immune conditions, inherited mutations and abnormal occurrence from metabolism due to loss of tumor suppressor genes (Parsa, 2012).

Currently, there are several treatments of breast cancer, such as chemotherapy (the use of tamoxifen, raloxifene and taxol), radiation therapy (brachytherapy), surgery (mastectomy), hormone therapy (aromatase inhibitor) or targeted therapy (herceptin). Chemotherapy is the most commonly used breast cancer treatment. Nevertheless, it comes with some adverse effects such as immunosuppression (Chapman et al., 2013), formation of secondary tumour (Powe et al., 2010) and development of cancer resistance (Glück, 2014). Therefore, alternative management for breast cancer is crucial to minimise the adverse effects.

The elimination of cancer cells is possible via induction of apoptosis and inhibition of cell cycle phase. Apoptosis is a programmed cell death, which is important in animal development, tissue homeostasis and other disease process (Yu et al., 2015) as the common response of cell stress induced by physiological changes, drugs, agents or toxins (Gerl and Vaux, 2005). The alterations of normal apoptotic pathways result in the process of neoplastic transformation, progression and metastasis (Elumalai et al., 2012). Apoptosis is a more preferred mode of cell death than necrosis because it is a programmed cell death and does not trigger inflammation (Millan and Huerta, 2009). Most of the antibreast cancer drugs induced apoptosis such as paclitaxel and doxorubicin (Lee et al., 2013), disulfiram (Chen et al., 2006), cannabidiol (Shrivastava et al., 2011), platinum II (Muscella et al., 2013) and tamoxifen (Liu et al., 2014). There are two types of apoptotic pathways, which are intrinsic and extrinsic pathway (Dasgupta et al., 2017; Ricci and Zhong, 2006). The extrinsic or receptor pathway is

initiated by binding of an extracellular ligand (such as FasL and TNF- α) to its receptor (such as FasR and TNFR). Next, an adaptor protein (such as FADD, TRADD and RIDD) transmits the activating signal to an initiator caspase (such as caspases-2, -8 and -10) (Dasgupta et al., 2017; Riedl and Shi, 2004). TNF- α is a potent cytokine in response to injury, inflammation, infection and other environmental challenges that result in apoptosis (MacParland et al., 2016; Baud and Karin., 2001). TNF- α is frequently detected in human cancer tissues such as breast, ovarian and renal cancer. TNF- α activation promotes a recruitment of adaptor protein and NF- κ B pathway (MacParland et al., 2016; Choi et al., 2013). NF- κ B participates in the development, survival, proliferation and metastasis in cancer (Park and Hong, 2016; Pandey et al., 2008). The free NF- κ B will be translocated from cytoplasm to the nucleus and bound to specific DNA sequences, which are related to tumor development and metastases (Park and Hong, 2016).

The intrinsic or mitochondria pathway is initiated within the cell by a few factors such as hypoxia, genetic damage, extremely high concentration of Ca^{2+} and severe oxidative stress via outer mitochondrial membrane permeabilization (Dasgupta et al., 2017; Wong, 2011; Riedl and Salvesen, 2007). Bcl-2 family of proteins initiates the mitochondrial apoptotic pathway by down-regulation of anti-apoptotic (such as Bcl-2, Bcl-X_L, Bcl-W, Bfl-1 and Mcl-1) and up-regulation of pro-apoptotic (such as Bax, Bak, Bad, Bcl-Xs, Bid, Bik, Bim and Hrk) protein (Wong, 2011). In both pathways, they will result in the activation of family cysteine proteases (caspases) that act in proteolytic cascade to dismantle and remove the dead cells (Czerski and Nunez, 2004). There are two classes of caspases, which are the initiator caspases (such as caspase 2, 8, 9 and 10) and the effector caspases (such as caspase 3, 6 and 7) (Kawai et al., 2004). Initiator caspases will initiate the caspase-cascade and activates the effector caspases that results in apoptosis (Faleiro et al., 1997). At the same time, apoptosis will eliminate the cancer cells (Dasgupta et al., 2017).

In cell cycle regulation, cyclin-dependent kinases (CDKs) and cyclins play the most critical role to control the growth and proliferation of cancer cells (Dasgupta et al., 2017). The disruption of the enzymes and proteins to form a complex by CDK inhibitor can facilitate apoptotic death (Dasgupta et al., 2017; Rastogi and Mishra, 2012).

Natural products are employed in the management of variety of ailments and diseases including cancer for thousands of years (Dias et al., 2012). Approximately, 75% of novel anticancer agents derived from natural products from 1981 to 2010 (Newmann and Cragg, 2012). Indeed, plants have been a good source of a few anticancer agents, especially for breast cancer treatment, such as vindesine from *Catharanthus roseus* (Cragg and Newman, 2005), taxol from *Taxus brevifolia* (Kingston, 2007), beta-lapachone from *Tabebuia avellanedae* (Li et al., 2000; De Almeida, 2009), berberine from *Berberineeris* species (Wang et al., 2011), genistein from *Glycin max* (Kingham et al., 2009) and silvestrol from *Aglaia foveolata* (Moon et al., 2006). The potential of natural compounds in readjusting the balance in cancer to favor apoptosis has caused people to turn to natural products as an alternative to chemotherapeutic drugs for the management of cancer (Boik, 2001).

Dryobalanops or locally known as Kapur is a type of flowering plant from *Dipterocarpaceae* family. There are only seven species worldwide restricted to West Malesia (Peninsular Malaysia, Borneo and Sumatra), which are *D. rappa*, *D. aromatica*, *D. beccarii*, *D. lanceolata*, *D. fusca*, *D. keithii* and *D. oblongifolia* (Ashton and Flora, 1983). This genus is a rich source of resveratrol oligomers (trans-3,4',5-trihydroxystilbene), which possess various bioactivities such as antioxidant (Fauconneau et al., 1997), anticancer (Dai et al., 1998) and antifungal (Pacher et al., 2002). There are several resveratrol oligomers isolated from *Dryobalanops* sp such as ampelopsin E (Oshima and Ueno, 1993), ampelopsin F (Takaya et al., 2002), flexuosol A (Li et al., 1998), laevifonol (Hirano et al., 2003), Malaysianol A (Wibowo et al., 2011b), Malaysianol D (Wibowo et al., 2014) and nepalensinol E (Yamada et al., 2006). Malaysianol A and ampelopsin E from *D. beccarii* were cytotoxic towards breast adenocarcinoma cell line, MCF-7 (Wibowo et al., 2014) but the mechanism of action is not yet studied.

1.2 Objective

1.2.1 General Objective

This study was conducted to determine the cytotoxicity of resveratrol oligomers of *Dryobalanops* species (ampelopsin E, ampelopsin F, flexuosol A, laevifonol, Malaysianol A, Malaysianol D and nepalensinol E) towards non-hormone dependent (MDA-MB-231) and hormone dependent (MCF-7) breast cancer, human colon cancer (HT-29), alveolar carcinoma (A-549), cervical adenocarcinoma (HeLa), non-tumorigenic epithelial breast (MCF-10A) and mouse embryonic fibroblast (NIH/3T3) cell lines.

1.2.2 Specific Objective

1. To determine the most cytotoxic resveratrol oligomer and the most sensitive cell line.
2. To determine the morphological changes of the most sensitive cell line treated with the most cytotoxic resveratrol oligomer.
3. To evaluate the mode of the cell death and cell cycle arrest induced by the most cytotoxic resveratrol oligomer in the most sensitive cell line.
4. To determine the effects of the most cytotoxic resveratrol oligomer on the expression of NF- κ B, p53, p21, Cyclin A, Cyclin B1, CDK1, Bax and Bcl-2 in the most sensitive cell line.

1.3 Hypothesis

All of the resveratrol oligomers of *Dryobalanops* species will exhibit cytotoxicity towards the cancer cell lines. The most cytotoxic resveratrol oligomer will induce apoptosis and cell cycle arrest in the the most sensitive cell line. The expression level of NF- κ B, p53, Cyclin A, Cyclin B1, CDK1 and Bcl-2 will decrease, whereas the expression level of p21 and Bax will increase following treatment with the most cytotoxic resveratrol oligomer.

REFERENCES

- Abbas, T., and Dutta, A. 2009. p21 in cancer: intricate networks and multiple activities. *Nature Reviews Cancer*. 9(6): 400-414.
- Ahmat, N., Wibowo, A., Mohamad, S.A.S., Low, A.L.M., Sufian, A.S., Yusof, M.I.M., and Latip, J. 2014. A new symmetrical tetramer oligostilbenoid containing tetrahydrofuran ring from the stem bark of *Dryobalanops lanceolata*. *Journal of Asian Natural Products Research*. 16(11): 1099-1107.
- Alami, N., Paterson, J., Belanger, S., Juste, S., Grieshaber, C.K., and Leyland-Jones, B. 2007. Comparative analysis of xanafide cytotoxicity in breast cancer cell lines. *British Journal of Cancer*. 97: 58-64.
- Alfarouk, O.K., Stock, C.M., Taylor, S., Walsh, M., Muddathir, A.K., Verduzco, D., Bashir, A.H.H., Mohammed, O.Y., Elhassan, G.O., Harguindey, S., Reshkin, S.J., Ibrahim, M.E., and Rauch, C. 2015. Resistance to cancer chemotherapy: failure in drug response from ADME to P-gp. *Cancer Cell International*. 15(71): 1-13.
- Alkhalaf, M. 2007. Resveratrol-induced growth inhibition in MDA-MB-231 breast cancer cells is associated with mitogen-activated protein kinase signaling and protein translation. *European Journal of Cancer Preventive*. 16(4): 334-341.
- Al-Qubaisi, M., Rozita, R., Yeap, S.K., Omar, A.R., Ali, A.M., and Alitheen, N.B. 2011. Selective cytotoxicity of goniothalamin against hepatoblastoma HepG2 cells. *Molecules*. 16(4): 2944-2959.
- Anand, P., Kunnumakara, A.B., Sundaram, C., Harikumar, K.B., Tharakan, S.T., Lai, O.S., Sung, B., and Aggarwal, B.B. 2008. Cancer is a preventable disease that requires major lifestyle changes. *Pharmaceutical Research*. 25(9): 2097-2116.
- Andre, F., and Zielinski, C.C. 2012. Optimal strategies for the treatment of metastatic triple-negative breast cancer with currently approved agents. *Annals of Oncology*. 23(6): 46-51.
- Arancibia, J.C., Bustos, C.E., Molina, A.C., Tapia, R.A., Faundez, M., Torres, M.J., Aguirre, A.M., and Salas, C.O. 2015. Synthesis and pharmacophore modeling of 2,6,9-trisubstituted purine derivatives and their potential role as apoptosis-inducing agents in cancer cell lines. *Molecules*. 20(4): 6808-6826.
- Archana, M., Bastian, Yogesh, T.L., and Kumaraswamy, K.L. 2013. Various methods available for detection of apoptotic cells. *Indian Journal of Cancer*. 50(3): 274-283.
- Ashkenazi, A., and Herbst, R.S. 2008. To kill a tumor cell: the potential of proapoptotic receptor agonists. *The Journal of Clinical Investigation*. 118(6): 1979-1990.

- Ashton, P.S. 1982. Dipterocarpaceae. In Van Steenis, C.G.G.J, ed. Flora Malesiana, volume 9. pp 237-552. Martinus Nijhoff Publishers: The Hague.
- Ashton, P.S., and Flora, A.A. 1983. Malesiana. *Spermatophyta I*. pp 391-436. Martinus Nijhoff Publishers: The Hague.
- Baeuerle, P.A., and Baltimore, D. 1996. NF-kappa B: ten years after. *Cell*. 87(1): 13-20.
- Banafsa, A.M., Roshan, S., Liu, Y., Zhao, S., Yang, G., He, G., and Chen, M. 2014. Fucoidan induces apoptosis in MDA-MB-231 cells by activating caspase cascade and down-regulating XIAP. *IOSR Journal of Pharmacy and Biological Sciences (IOSR-JPBS)*. 9(3): 59-64.
- Barjot, C., Tournaire, M., Castagnino, C., Vigor, C., Vercauteren, J., and Rossi, J.F. 2007. Evaluation of antitumor effects of two vine stalk oligomers of resveratrol on a panel of lymphoid and myeloid cell lines: comparison with resveratrol. *Life Sciences*. 81(23-24): 1565-1574.
- Bastian, A.M., Yogesh, T.L., and Kumaraswamy, K.L. 2013. Various methods available for detection of apoptotic cells. *Indian Journal of Cancer*. 50(3): 274-283.
- Baud, V., and Karin, M. 2001. Signal transduction by tumor necrosis factor and its relatives. *Trends in Cell Biology*. 11(9): 372-377.
- Bendris, N., Lemmers, B., Blanchard, J.M., and Arsic, N. 2011. Cyclin A2 mutagenesis analysis: a new insight into CDK activation and cellular localization requirements. *PLOS ONE*. 6(7): 1-9.
- Bertheau, P., Lehmann-Che, J., Varna, M., Dumay, A., Poirot, B., Porcher, R., Turpin, E., Plassa, L.F., Roquancourt, A.D., Boursstyn, E., Cremoux, P.D., Janin, A., Giacchetti, S., Espie, M., dan The, H.D. 2013. p53 in breast cancer subtypes and new insights into response to chemotherapy. *Breast*. 22(2013): 27-29.
- Berthois, Y., Katzenellenbogen, J.A., and Katzenellenbogen, B.S. 1986. Phenol red in tissue culture media is a weak estrogen: implications concerning the study of estrogen-responsive cells in culture. *Proceedings of the National Academy of Sciences of the United States of America*. 83(8): 2496-2500.
- Bertucci, F., Finetti, P., Cervera, N., Esterni, B., Hermitte, F., Viens, P., and Birnbaum, D. 2008. How basal are triple negative breast cancers? *International Journal of Cancer*. 123(1): 236-240.
- Boik, J. 2001. Natural compounds in cancer therapy. pp 2-3. Oregon Medical Press LLC: Princeton, Minnesota, USA.
- Boralle, N., Gottlieb, H.E., Gottlieb, O.R., Kubitzki, K., Lopes, L.M.X., Yoshida, M., and Young, M.C.M. 1993. Oligostilbenoids from *Gnetum venosum*. *Phytochemistry*. 34(5): 1403-1407.

- Bradford, M.M. 1976. A rapid and sensitive method for the quantitation of microgram quantities of protein utilizing the principle of protein-dye binding. *Analytical Biochemistry*. 7(72): 248-254.
- Brady, C.A, and Attardi, L.D. 2010. p53 at a glance. *Journal of Cell Sciences*. 123(15): 2527-2532.
- Brown, J.M., and Attardi, L.D. 2005. The role of apoptosis in cancer development and treatment response. *Nature Reviews: Cancer*. 5(3): 231-238.
- Burger, A.M., and Fiebig, H.H. 2004. Preclinical screening for new anticancer agents. pp 29-44. *Handbook of Anticancer Pharmacokinetics and Pharmacodynamics*, Humana Press Inc: Totowa, NJ.
- Cabrera, M., Gomez, N., Lenicov, F.R., Echeverria, E., Shayo, C., Moglioni, A., Fernandez, N., and Davio, C. 2015. G2/M cell cycle arrest and tumor selective apoptosis of acute leukemia cells by a promising benzophenone thiosemicarbazone compound. *PLOS ONE*. 10(9): 1-21.
- Campbell, C.T., Prince, M., Landry, G.M., Kha, V., and Kleiner, H.E. 2007. Pro-apoptotic effects of 1'-acetoxychavicol acetate on in human breast carcinoma cells. *Toxicology Letter*. 173(3): 151-160.
- Campisi, J. 2013. Aging, cellular senescence, and cancer. *Annual Review of Physiology*. 75: 685-705.
- Cao, Y.J., Zhou, Y.J., He, X.Z., Zhou, C.X., Cui, L., Zhuang, Q.F., and Xu, R.F. 2017. Overexpression of β -arrestin2 induces G1-phase cell cycle arrest and suppresses tumorigenicity in renal cell carcinoma. *European Review for Medical and Pharmacological Sciences*. 21(8): 1729-1737.
- Chan, F.K.M., Moriwaki, K., and Rosa, M.J.D. 2013. Detection of necrosis by release of lactate dehydrogenase (LDH) activity. *Methods in Molecular Biology*. 979: 65-70.
- Chandler, H., and Peter, G. 2013. Stressing the cell cycle in senescence and aging. *Current Opinion in Cell Biology*. 25(6): 765-771.
- Chapman, J.R., Webster, A.C., and Wong, G. 2013. Cancer in the transplant recipient. *Cold Spring Harb Perspect Medicine*. 3: 1-16.
- Chaturvedi, M.M., Sung, B., Yadav, V.R., Kannappan, R., and Aggarwal, B.B. 2011. NF- κ B addiction and its role in cancer: 'one size does not fit all'. *Oncogene*. 30(14): 1615-1630.
- Chavez, K.J., Gamirella, S.V., and Lipkowitz, S. 2010. Triple negative breast cancer cell lines: One tool in the search for better treatment of triple negative breast cancer. *Breast Disease*. 32(1-2): 35-48.

- Chen, A., Huang, X., Xue, Z., Cao, D., Huang, K., Chen, J., Pan, Y., and Gao, Y. 2015. The role of p21 in apoptosis, proliferation, cell cycle arrest, and antioxidant activity in UVB-irradiated human HaCaT keratinocytes. *Medical Science Monitor Basic Research*. 21: 86-95.
- Chen, D., Cui, Q.C., Yang, H., and Dou, Q.P. 2006. Disulfiram, a clinically used anti-alcoholism drug and copper-binding agent, induces apoptotic cell death in breast cancer cultures and xenografts via inhibition of the proteasome activity. *Cancer Research*. 66(21): 10425-10433.
- Chen, J.C., Chang, N.W., Chung, J.G., and Chen, K.C. 2003. Saikosaponin-A induces apoptotic mechanism in human breast MDA-MB-231 and MCF-7 cancer cells. *American Journal of Chinese Medicine*. 31(3): 363-377.
- Cheng, Y.C., and Prusoff, W.H. 1973. Relationship between the inhibition constant (KI) and the concentration of inhibitor which causes 50 per cent inhibition (I50) of an enzymatic reaction. *Biochemical Pharmacology*. 22(23): 3099-3108.
- Choi, Y.K., Cho, S.G., Woo, S.M., Yun, Y.J., Jo, J., Kim, W., Shin, Y.C., and Ko, S.G. 2013. *Saussurea lappa clarke*-derived costunolide prevents TNF α -induced breast cancer cell migration and invasion by inhibiting NF- κ B activity. *Evidence-Based Complementary and Alternative Medicine*. 2013: 1-10.
- Christofferson, D.E., and Yuan, J. 2010. Cyclophilin A release as a biomarker of necrotic cell death. *Cell Death and Differentiation*. 17(12): 1942-1943.
- Chu, I.M., Lai, W.C., Aprelikova, A., El Touny, L.H., Kourus-Mehr, H., and Green, J.E. 2013. Expression of GATA3 in MDA-MB-231 Triple negative breast cancer cells induces a growth inhibitory response to TGF β . *PLOS ONE*. 8(4): 1-13.
- Coffill, C.R., Lee, A.P., Siau, J.W., Chee, S.M., Joseph, T.L., Tan, Y.S., Madhumalar, A., Tay, B.H., Brenner, S., Verma, C.S., Ghadessy, F.J., Venkatesh, B., and Lane, D.P. 2016. The p53-Mdm2 interaction and the E3 ligase activity of Mdm2/Mdm4 are conserved from lampreys to human. *Genes and Development*. 30(3): 281-292.
- Coffill, C.R., Muller, P.A., Oh, H.K., Neo, S.P., Hogue, K.A., Cheok, C.F., Vousden, K.H., Lane, D.P., Blackstock, W.P., and Gunaratne, J. 2012. Mutant p53 interactome identifies nardilysin as a p53R273H-specific binding partner that promotes invasion. *EMBO Reports*. 13(7): 638-644.
- Collignon, J., Lousberg, L., Schroeder, H., and Jerusalem, G. 2016. Triple negative breast cancer: treatment challenges and solutions. *Breast Cancer: Target and Therapy*. 20(8): 93-107.
- Collins, K., Jacks, T., and Pavletich, N.P. 1997. The cell cycle and cancer. *Proceedings of the National Academy of Sciences*. 94(7): 2776-2778.
- Cragg, G.M., and Newman, D.J. 2005. Plants as a source of anti-cancer agents. *Journal of Ethnopharmacology*. 100(1-2): 72-79.

- Czerski, L., and Nunez, G. 2004. Apoptosome formation and caspase activation: is it different in the heart? *Journal of Molecular and Cellular Cardiology*. 37(3): 643-652.
- Dai, J.R., Hallockm, Y.F., Cardellina, J.H.II and Boyd, M.R. 1998. HIV inhibitory and cytotoxic oligostilbenes from the leaves of *Hopea malibato*. *Journal of Natural Products*. 61(3): 351-353.
- Dasgupta, A., Nomura, M., Shuck, R., and Yustein, J. 2017. Cancer's achilles' heel: apoptosis and necroptosis to the rescue. *International Journal of Molecular Sciences*. 18(23): 1-20.
- De Almeida, E.R. 2009. Preclinical and clinical studies of lapachol and beta-lapachone. *Open Natural Products Journal*. 8(2): 42-47.
- De Boer, L., Oakes, V., Beamish, H., Giles, N., Stevens, F., Somodevilla-Torres, M., Desouza, C., and Gabrielli, B. 2008. Cyclin A/cdk2 coordinates centrosomal and nuclear mitotic events. *Oncogene*. 27(31): 4261-4268.
- Dewson, G., and Kluc, R.M. 2010. Bcl-2 family-regulated apoptosis in health and disease. *Cell Health and Cytoskeleton*. 2010(2): 9-22.
- Di Agostino, S., Strano, S., Emiliozzi, V., Zerbini, V., Mottolese, M., Sacchi, A., Blandino, G., and Piaggio, G. 2006. Gain of function of mutant p53: the mutant p53/NF-Y protein complex reveals an aberrant transcriptional mechanism of cell cycle regulation. *Cancer Cell*. 10(3): 191-202.
- Dias, D.A., Urban, S., and Roessner, U. 2012. A historical overview of natural products in drug discovery. *Metabolites*. 2(2): 303-336.
- Dickens, L.S., Powley, I.R., Hughes, M.A., and MacFarlane, M. 2012. The "complexities" of life and death: Death receptor signalling platforms. *Experimental Cell Research*. 318(11): 1269-1277.
- Dickson, M.A., and Schwartz, G.K. 2009. Development of cell-cycle inhibitors for cancer therapy. *Current Oncology*. 16(2): 36-43.
- Dumay, A., Feugeas, J.P., Wittmer, E., Lehmann-Che, J., Bertheau, P., Espié, M., Plassa, L.F., Cottu, P., Marty, M., André, F., Sotiriou, C., Pusztai, L., and de Thé, H. 2013. Distinct TP53 mutants in breast cancers subgroups. *International Journal of Cancer*. 132(5):1227-1231.
- El-Deiry, W.S. 2016. p21(WAF1) mediates cell cycle inhibition, relevant to cancer suppression and therapy. *Cancer Research*. 76(18): 5189-5191.
- Elmore, S. 2007. Apoptosis: A review of programmed cell death. *Toxicologic Pathology*. 35(4): 495-516.

- Elumalai, P., Gunadharini, D.N., Senthilkumar, K., Banudevi, S., Arunkumar, R., Benson, C.S., Sharmila, G., and Arunakaran, J. 2012. Induction of apoptosis in human breast cancer cells by nimbolide through extrinsic and intrinsic pathway. *Toxicology Letters*. 215(2): 131-142.
- Estaquier, J., Vallette, F., Vayssiere, J.L., and Mignotte, B. 2012. The mitochondrial pathways of apoptosis. *Advances in Experimental Medicine and Biology*. 942: 157-183.
- Faleiro, L., Kobayashi, R., Fearnhead, H., and Lazebnik, Y. 1997. Multiple species of CPP32 and Mch2 are the major active caspases present in apoptotic cells. *EMBO Journal*. 16(9): 2271-2281.
- Fanoodi, T.S., Motalleb, G., Moghandam, A.Y., and Talaei, R. 2015. *p21* gene expression evaluation in esophageal cancer patients. *Gastro Intestinal Tumors*. 2: 144-164.
- Fauconneau, B., Waffo-Teguo, P., Huguet, F., Barrier, L., Decendit, A., and Merillon, J.M. 1997. Comparative study of radical scavenger and antioxidant properties of phenolic compounds from *Vitis vinifera* cell cultures using *in vitro* tests. *Life Sciences*. 61(21): 2103-2110.
- Feher, M., and Schmidt, J.M. 2003. Property distributions: Differences between drugs, natural products, and molecules from combinatorial chemistry. *Journal of Chemical Information and Computer Sciences*. 43(1): 218-227.
- Ferlay, J., Soerjomataram, I., Dikshit, R., Eser, S., Mathers, C., Rebelo, M., Parkin, D.M., Forman, D., and Bray, F. 2015. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *International Journal of Cancer*. 136(5): 359-386.
- Florea, A.M., and Busselberg, D. 2011. Cisplatin as an anti-tumour drug: Cellular mechanism of activity, drug resistance and induced side effects. *Cancers*. 3(1): 1351-1371.
- Fogh, J., and Trempe, G. 1975. New human tumor cell lines. ed. Fogh J. Human tumor cell *in vitro*. pp 115-159. Springer, New York.
- Fulda, D., and Debatin, K.M. 2006. Extrinsic versus intrinsic apoptosis pathways in anticancer chemotherapy. *Oncogene*. 25(34): 4798-4811.
- Fulda, S. 2008. Betulinic acid for cancer treatment and prevention. *International Journal of Molecular Sciences*. 9(6): 1096-1107.
- Gambini, J., Ingles, M., Olaso, G., Lopez-Grueso, R., Bonet-Costa, V., Gimeno-Mallench, L., Mas-Bargues, C., Abdelaziz, K.M., Gomez-Cabrera, M.C., Vina, J., and Borras, C. 2015. Properties of resveratrol: *In vitro* and *in vivo* studies about metabolism, bioavailability, and biological effects in animal models and humans. *Oxidative Medicine and Cellular Longevity*. 2015: 1-13.

- Gerl, R., and Vaux, D.L. 2005. Apoptosis in the development and treatment of cancer. *Carcinogenesis*. 26(2): 263-270.
- Giampietri, C., Starace, D., Petrungaro, S., Filippini, A., and Ziparo, E. 2014. Necroptosis: molecular signalling and translational implications. *International Journal of Cell Biology*. 2014: 1-6.
- Giard, D.J., Aaronson, S.A., and Todaro, G.J. 1973. *In vitro* cultivation of human tumors: establishment of cell lines derived from a series of solid tumors. *Journal of the National Cancer Institute*. 51(5): 1417-1423.
- Giono, L.E., and Manfredi, J.J. 2007. Mdm2 is required for inhibition of CDK2 activity by p21, thereby contributing to p53-dependent cell cycle arrest. *Molecular and Cellular Biology*. 27(11): 4166-4178.
- Gluck, S. 2014. Extending the clinical benefit of endocrine therapy for women with hormone receptor-positive metastatic breast cancer: differentiating mechanisms of action. *Clinical Breast Cancer*. 14(2): 75-84.
- Gottwald, H., and Parameswaran, N. 1966. Das sekundäre xylem der Familie Dipterocarpaceae. Anatomische untersuchungen zur taxonomie und phylogenie. *Dotanische Jahrbucher*. 85(3): 410-508.
- Gray, E.M., Diaz-Vazquez, G., Veatch, S.L. 2015. Growth conditions and cell cycle phase modulate phase transition temperatures in RBL-2H3 derived plasma membrane vesicles. *PLOS ONE*. 10(9): 1-16.
- Hanahan, D., and Weinberg, R.A. 2000. The hallmarks of cancer. *Cell*. 100(1): 57-70.
- Hartman, Z.C., Poage, G.M., Hollander, P.D., Tsimelzon, A., Hill, J., Panupinthu, N., Zhang, Y., Mazumdar, A., Hilsenbeck, S.G., Mills, G.B., and Brown, P.H. 2013. Growth of triple-negative breast cancer cells relies upon coordinate autocrine expression of the pro-inflammatory cytokines IL-6 and IL-8. *Cancer Research*. 73(11): 1-19.
- Hassan, M., Watari, H., Almaaty, A.A., Ohba, Y., and Sakuragi, N. 2014. Apoptosis and molecular targeting therapy in cancer. *BioMed Research International*. 2014: 1-23.
- Hirano, Y., Kondo, R., and Sakai, K. 2003. Novel stilbenoids isolated from heartwood of *Shorea laevifolia*. *Journal of Wood Science*. 49(1): 53-58.
- Hoesel, B., and Schmid, J.A. 2013. The complexity of NF- κ B signaling in inflammation and cancer. *Molecular Cancer*. 12(86): 1-15.
- Holiday, D.L., and Speirs, V. 2011. Choosing the right cell lines for breast cancer research. *Breast Cancer Research*. 13(4): 215-222.

- Hollmann, G., Linden, R., Giangrande, A., and Allodi, S. 2016. Increased p53 and decreased p21 accompany apoptosis induced by ultraviolet radiation in the nervous system of crustacean. *Aquatic Toxicology*. 173: 1-8.
- Hong, Y.B., Kang, H.J., Kim, H.J., Rosen, E.M., Dakshanamurthy, S., Rondanin, R., Baruchello, R., Grisolia, G., Daniele, S., and Bae, I. 2009. Inhibition of cell proliferation by a resveratrol analog in human pancreatic and breast cancer cells. *Experimental and Molecular Medicine*. 41: 151-160.
- Huang, H., Hu, M., Zhao, R., Li, P., and Li, M. 2013. Dihydromyricetin suppresses the proliferation of hepatocellular carcinoma cells by inducing G₂/M arrest through the Chk1, Chk2/Cdc25C pathway. *Oncology Reports*. 30(5): 2467-2475.
- Hudis, C.A., and Gianni, L. 2011. Triple-negative breast cancer: an unmet medical need. *Oncologist*. 16(1): 1-11.
- Hui, L., Zheng, Y., Yan, Y., Bargonetti, J., and Foster, D.A. 2006. Mutant p53 in MDA-MB-231 breast cancer cells is stabilized by elevated phospholipase D activity and contributes to survival signals generated by phospholipase D. *Oncogene*. 25(55): 7305-7310.
- Igney, F.H., and Krammer, P.H. 2002. Death and anti-death: tumor resistance to apoptosis. *Nature Reviews: Cancers*. 2(4): 277-288.
- Jäger, W., Gruber, A., Giessrigl, B., Krupitza, G., Szekeres, T., and Sonntag, D. 2011. Metabolomic analysis of resveratrol-induced effects in the human breast cancer cell lines MCF-7 and MDA-MB-231. *OMICS*. 15(1-2): 9-14.
- Jain, M.V., Paczulla, A.M., Klonisch, T., Dimgba, F.N., Rao, S.B., Roberg, K., Schweizer, F., Lengerke, C., Davoodpour, P., Palicharla, V.R., Maddika, S., and Los, M. 2013. Interconnections between apoptotic, autophagic and necrotic pathways: implications for cancer therapy development. *Journal of Cellular and Molecular Medicine*. 17(1): 12-29.
- Kado, K., Forsyth, A., Patel, P.R., and Schwartz, J.A. 2012. Dietary supplements and natural products in breast cancer trials. *Frontiers in Bioscience*. 4(1): 546-567.
- Kaplan, A., Ciftci, G.A., and Kutlu, H.M. 2017. The apoptotic and genomic studies on A-549 cell line induced by silver nitrate. *Tumor Biology*. 2017: 1-17.
- Karimian, A., Ahmadi, Y., and Yousefi, B. 2016. Multiple functions of p21 in cell cycle, apoptosis and transcriptional regulation after DNA damage. *DNA Repair*. 42: 63-71.
- Karimian, H., Moghadamtousi, S.Z., Fadaeinasab, M., Golbabapour, S., Razavi, M., Hajrezaie, M., Arya, A., Abdulla, M.A., Mohan, S., Ali, H.M., and Noordin, M.I. 2014. *Ferulago angulata* activates intrinsic pathway of apoptosis in MCF-7 cells associated with G₁ cell cycle arrest via involvement of p21/p27. *Drug Design, Development and Therapy*. 8: 1481-1497.

- Kavsan, V.M., Lershov, A.V., and Balynska, O.V. 2011. Immortalized cells and one oncogene in malignant transformation: old insights on new explanation. *BioMed Central Cell Biology*. 12(23): 1-2.
- Kawai, H., Suzuki, T., Kobayashi, T., Mizuguchi, H., Hayakawa, T., and Kawanishi, T. 2004. Simultaneous imaging of initiator/effector caspase activity and mitochondrial membrane potential during cell death in living HeLa cells. *Biochemica et Biophysica Acta (BBA)-Molecular Cell Research*. 1693(2): 101-110.
- Kearney, T., Hughes, A., Hanson, R.N., and DeSombre, E.R. 1999. Radioactivity of Auger electron-emitting estrogens in MCF-7 spheroids: A potential treatment for estrogen receptor-positive tumors. *Radiation Research*. 151(5): 570-579.
- Kennecke, H., Yerushalmi, R., Woods, R., Cheang, M.C., Voduc, D., Speers, C.H., Nielsen, T.O., and Gelmon, K. 2010. Metastatic behavior of breast cancer subtypes. *Journal of Clinical Oncology*. 28(20): 3271-3278.
- Kerr, J.F.R., Wyllie, A.H., and Currie, A.R. 1972. Apoptosis: A basic biological phenomenon with wide ranging implications in tissue kinetics. *British Journal of Cancer*. 26(4): 239-257.
- Khodapasand, E., Jafarzadeh, N., Farrokhi, F., Kamalidehghan, B., and Houshmand, M. 2015. Is Bax/Bcl-2 ratio considered as a prognostic marker with age and tumor location in colorectal cancer? *Iranian Biomedical Journal*. 19(2): 69-75.
- Kim, J.A., Kim, D.H., Hossain, M.A., Kim, M.Y., Sung, B., Yoon, J.H., Suh, H., Jeong, T.C., Chung, H.Y., and Kim, N.D. 2014. HS-1793, a resveratrol analogue, induces cell cycle arrest and apoptotic cell death in human breast cancer cells. *International Journal of Oncology*. 44: 473-480.
- Kim, J.Y., Jung, H.H., Ahn, S., Bae, S.Y., Lee, S.K., Kim, S.W., Lee, J.E., Nam, S.J., Ahn, J.S., Im, Y.H., and Park, Y.H. 2016. The relationship between nuclear factor (NF)- κ B family gene expression and prognosis in triple negative breast cancer (TNBC) patients receiving adjuvant doxorubicin treatment. *Scientific Reports*. 6(31804): 1-11.
- Kinghorn, D.A., de Blanco, E.J.C., Chai, H.B., Orjala, J., Farnsworth, N.R., Soejarto, D.D., Oberlies, N.H., Wani, M.C., Kroll, D.J., Pearce, C.J., Swanson, S.M., Kramer, R.A., Rose, W.C., Fairchild, C.R., Vite, G.D., Emanuel, S., Jarjoura, D., and Cope, F.O. 2009. Discovery of anticancer agents of diverse natural origin. *Pure and Applied Chemistry*. 81(6): 1051-1063.
- Kingston, D.G.I. 2007. The shape of things to come: structural and synthetic studies of taxol and related compounds. *Phytochemistry*. 68(14): 1844-1854.
- Kong, Y., Chen, J., Zhou, Z., Xia, H., Qiu, M.H., and Chen, C. 2014. Cucurbitacin E induces cell cycle G2/M phase arrest and apoptosis in triple negative breast cancer. *PLoS ONE*. 9(7): 1-8.

- Kroemer, G., Galluzzi, L., and Brenner, C. 2007. Mitochondrial membrane permeabilization in cell death. *Physiological Reviews*. 87(1): 99-163.
- Krol, S.K., Kielbus, M., Rivero-Muller, A., and Stepulak, A. 2015. Comprehensive review on betulin as a potent anticancer agent. *BioMed Research International*. 2015: 1-11.
- Krysko, D.V., Berghe, T.V., Parthoens, E., D'Herde, K., and Vandenabeele, P. 2008. Methods for distinguishing apoptotic from necrotic cells and measuring their clearance. *Methods in Enzymology*. 442: 307-341.
- Kundaje, A., and Eisenman, S. 2001. Modeling of the P53 pathway to cell cycle arrest and apoptosis: Relevance to cancer. Project for ELEN E6901: Computational Modeling of Genetic and Biochemical Networks. 1-19.
- Lakhani, S.R., van de Vijver, M.J., Jacquemier, J., Anderson, T.J., Osin, P.P., McGuffog, L., and Easton, D.F. 2002. The pathology of familial breast cancer: predictive value of immunohistochemical markers estrogen receptor, progesterone receptor, HER-2, and p53 in patients with mutations in *BRCA1* and *BRCA2*. *Journal of Clinical Oncology*. 20(9): 2310-2318.
- Lane, D.P. 1999. Exploiting the p53 pathway for cancer diagnosis and therapy. *British Journal of Cancer*. 80(1): 1-5.
- Lee, H.H., Ye, S., Li, X.J., Lee, K.B., Park, M.H., and Kim, S.M. 2013. Combination treatment with paclitaxel and doxorubicin inhibits growth of human esophageal squamous cancer cells by inactivation of Akt. *Oncology Reports*. 31(1): 138-188.
- Lee, J.S., and Oh, M. 2014. Reproductive factors and subtypes of breast cancer defined by estrogen receptor, progesterone receptor and human epidermal growth factor receptor 2: A register-based study from Korea. *Clinical Breast Cancer*. 14(6): 426-434.
- Lee, R.H., Yoon, N., Reneau, J.C., and Prockop, D.J. 2012. Preactivation of human MSCs with TNF-alpha enhances tumor-suppressive activity. *Cell Stem Cell*. 11(6): 825-835.
- Li, W.W., Li, B.G., and Chen, Y.Z. 1998. Flexuosol A, a new tetrastilbene from *Vitis flexuosa*. *Journal of Natural Products*. 61(5): 646-647.
- Li, Y., Li, C.J., Yu, D., and Pardee, A.B. 2000. Potent induction of apoptosis by β -lapachone in human multiple myeloma cell lines and patient cells. *Molecular Medicine*. 6(12): 1008-1015.
- Li, Y., Upadhyay, S., Bhuiyan, M., and Sarkar, F.H. 1999. Induction of apoptosis in breast cancer cells MDA-MB-231 by genistein. *Oncogene*. 18: 3166-3172.
- Liberti, M.V., and Locasale, J.W. 2016. The Warburg effect: How does it benefit cancer cells? *Trends in Biochemical Sciences*. 41(3): 211-217.

- Lim, K.G., Gray, A.I., Pyne, S., and Pyne, N.G. 2012. Resveratrol dimers are novel sphingosine kinase 1 inhibitors and affect sphingosine kinase 1 expression and cancer cell growth and survival. *British Journal of Pharmacology*. 166: 1605-1616.
- Lin, C.Y., Hsiao, W.C., Wright, D.E., Hsu, C.L., Lo, Y.C., Hsu, G.S.W., and Kao, C.F. 2013. Resveratrol activates the histone H2B ubiquitin ligase, RNF20, in MDA-MB-231 breast cancer cells. *Journal of Functional Foods*. 5(2): 790-800.
- Liou, G-Y., and Storz, P. 2010. Reactive oxygen species in cancer. *Free Radical Research*. 44(5): 479-496.
- Liu, C.Y., Hung, M.H., Wang, D.S., Chu, P.Y., Su, J.C., Teng, T.H., Huang, C.T., Chao, T.T., Wang, C.Y., Shiau, C.W., Tseng, L.M., and Chen, K.F. 2014. Tamoxifen induces apoptosis through cancerous inhibitor of protein phosphatase 2A-dependent phosphor-Akt inactivation in estrogen receptor-negative human breast cancer cells. *Breast Cancer Research*. 16(5): 431-446.
- Liu, X., Chen, B., Chen, L., Ren, W.T., Liu, J., Wang, G., Fan, W., Wang, X., and Wang, Y. 2013. U-shape suppressive effect of phenol red on the epileptiform burst activity via activation of estrogen receptors in primary hippocampal culture. *PLOS ONE*. 8(4): 1-9.
- Locuson, C.W., and Wahlstrom, J.L. 2005. Three-dimensional quantitative structure-activity relationship analysis of cytochromes P450: effects of incorporating higher affinity ligands and potential new applications. *Drug Metabolism and Disposition*. 33(7): 873-878.
- MacParland, S.A., Ma, X.Z., Chen, L., Khattar, R., Cherepanov, V., Selzner, M., Feld, J.J., Selzner, N., and McGivray, D. 2016. Lipopolysaccharide and tumor necrosis factor alpha inhibit interferon signaling in hepatocytes by increasing ubiquitin-like pretease 18 (USP18) expression. *Journal of Virology*. 90(12): 5549-5560.
- Mandang, Y.I., and Kagemori, N. 2004. A fossil wood of Dipterocarpaceae from Pliocene deposit in the west region of Java Island, Indonesia. *Journal of Biodiversity*. 5(1): 28-35.
- Martinez-Maqueda, D., Miralles, B., and Recio, I. 2015. HT29 cell line, ed. Verhoeckx et al. The impact of food bioactives on health. pp 113-124. Springer, Cham.
- Mason, E.F., and Rathmell, J.C. 2011. Cell metabolism: an essential link between cell growth and apoptosis. *Biochimica et Biophysica Acta*. 1813(4): 645-654.
- Maury, G. 1978. Dipterocarpacees: du fruit a la plantule. Ph.D Thesis. Toulouse. Universite Paul Sabatier.
- Mendes, T.F.S., Klusken, L.D., and Rodrigues, L.R. 2015. Triple negative breast cancer: Nanosolutions for a big challenge. *Advanced Science*. 2(11):1-15.

- Michael, D., and Oren, M. 2003. The p53-Mdm2 module and the ubiquitin system. *Seminars in Cancer Biology*. 13(1): 49-58.
- Millan, A., and Huerta, S. 2009. Apoptosis-inducing factor and colon cancer. *Journal of Surgical Research*. 151(1): 163-170.
- Miller, S.C., Huang, R., Sakamuru, S., Shukla, S.J., Attene-Ramos, M.S., Shinn, P., Leer, D.V., Leister, W., Austin, C.P., and Xia, M. 2010. Identification of known drugs that act as inhibitors of NF- κ B signaling and their mechanism of action. *Biochemical Pharmacology*. 79: 1272-1280.
- Mirzayans, R., Andrais, B., Scott, A., and Murray, D. 2012. New insights to p53 signaling and cancer cell response to DNA damage: implications for cancer therapy. *Journal of Biomedicine and Biotechnology*. 2012: 1-16.
- Mittelman, D., and Wilson, J.H. 2013. The fractured genome of HeLa cells. *Genome Biology*. 14: 111-114.
- Mohan, S., Abdelwahab, S.I., Kamalidehghan, B., Syam, S., May, K.S., Harmal, N.S.M., Shafifiyaz, N., Hadi, A.H.A., Hashim, N.M., and Rahmani, M. 2012. Involvement of NF- κ B and Bcl2/Bax signaling pathways in the apoptosis of MCF7 cells induced by a xanthone compound Pyranocycloartobiloxanthone A. *Phytomedicine*. 19(11): 1007-1015.
- Moon, Y.J., Wang, X., and Morris, M.E. 2006. Dietary flavonoids: effects on xenobiotic and carcinogen metabolism. *Toxicology In Vitro*. 20(2): 187-210.
- Mosmann, T. 1983. Rapid colorimetric assay for cellular growth and survival: application to proliferation and cytotoxicity assays. *Journal of Immunological Methods*. 65(1): 55-63.
- Muller, P.A.J., and Vousden, K.H. 2014. Mutant p53 in cancer: New functions and therapeutic opportunities. *Cancer Cell*. 25(3): 304-317.
- Muscella, A., Vetrugno, C., Fanizzi, F.P., Manca, C., De Pascali, S.A., and Marsigliante, S. 2013. A new platinum (II) compound anticancer drug candidate with selective cytotoxicity for breast cancer cells. *Cell Death and Disease*. 4(9): 796-806.
- Naseri, M.H., Mahdavi, M., Davoodi, J., Tackallou, S.H., Goudarzvand, M., and Neishabouri, S.H. 2015. Up regulation of Bax and down regulation of Bcl2 during 3-NC mediated apoptosis in human cancer cells. *Cancer Cell International*. 15(55): 1-9.
- Negrini, S., Gorgoulis, V.G., and Halazonetis, T.D. 2010. Genomic instability-an evolving hallmark of cancer. *Nature Review Molecular Cell Biology*. 11(3): 220-228.

- Neve, R.M., Chin, K., Fridlyand, J., Yeh, J., Baehner, F.L., Fevr, T., Clark, L., Bayani, N., Coppe, J.P., Tong, F., Speed, T., Spellman, P.T., DeVries, S., Lapuk, A., Wang, N.J., Kuo, W.L., Stilwell, J.L., Pinkel, D., Albertson, D.G., Waldman, F.M., McCormick, F., Dickson, R.B., Johnson, M.D., Lippman, M., Ethier, S., Gazdar, A., and Gray, J.W. 2006. A collection of breast cancer cell lines for the study of functionally distinct cancer subtypes. *Cancer Cells*. 10(6): 515-527.
- Newman, D.J., and Cragg, G.M. 2012. Natural products as sources of new drugs over the 30 years from 1981 to 2010. *Journal of Natural Products*. 75(3): 311-335.
- Nguyen, T.H., Mustafa, F.B., Pervaiz, S., Ng, F.S., and Lim, L.H. 2008. ERK1/2 activation is required for resveratrol-induced apoptosis in MDA-MB-231 cells. *International Journal of Oncology*. 33(1): 81-92.
- Nikolotopoulou, V., Markaki, M., Palikaras, K., and Tavernarakis, N. 2013. Crosstalk between apoptosis, necrosis and autophagy. *Biochimica et Biophysica Acta*. 1833(12): 3448-3456.
- Niu, W., Wu, P., Chen, F., Wang, J., Shang, X., and Xu, C. 2017. Discovery of selective cystathione β -synthase inhibitors by high-throughput screening with a fluorescent thiol probe. *Medicinal Chemistry Communications*. 8(1): 198-201.
- Nunes, T., Bernardazzi, C., and de Souza, H.S. 2014. Cell death and inflammatory bowel disease: apoptosis, necrosis and autophagy in the intestinal epithelium. *BioMed Research International*. 2014: 1-12.
- Ong, C.C., Gierke, S., Pitt, C., Sagolla, M., Cheng, C.K., Zhou, W., Jubb, A.M., Strickland, L., Schmidt, M., Duron, S.G., Campbell, D.A., Zheng, W., Dehdashti, S., Shen, M., Yang, N., Behnke, M.L., Huang, W., McKew, J.C., Chernoff, J., Forest, W.F., Haverty, P.M., Chin, S.F., Rakha, E.A., Green, A.R., Ellis, I.A., Caldas, C., O'Brien, T., Friedman, L.S., Koeppen, H., Rudolph, J., and Hoeflich, K.P. 2015. Small molecule inhibition of group I p21-activated kinases in breast cancer induces apoptosis and potentiates the activity of microtubule stabilizing agents. *Breast Cancer Research*. 17(59): 1-12.
- Osborne, C.K., Hobbs, K., and Clark, G.M. 1985. Effects of estrogens and antiestrogens on growth of human breast cancer cells in athymic nude mice. *Cancer Research*. 45(2): 584-590.
- Oshima, Y., and Ueno, Y. 1993. Ampelopsins D, E, H and cis-ampelopsin E, oligostilbenes from *Ampelopsis brevipedunculata* var. *Hancei* roots. *Phytochemistry*. 33(1): 179-182.
- Osman, A.M.M., Bayoumi, H.M., Al-Harathi, S.E., Damanhour, Z.A., and ElShal, M.F. 2012. Modulation of doxorubicin cytotoxicity by resveratrol in a human breast cancer cell line. *Cancer Cell International*. 12(46): 1-8.
- Otto, T., and Sicinski, P. 2017. Cell cycle proteins as promising targets in cancer therapy. *Nature Reviews Cancer*. 17: 93-115.

- Ouhtit, A., Gaur, R.L., Abdraboh, M., Ireland, S.K., Rao, P.N., Raj, S.G., Al-Riyami, H., Shanmuganathan, S., Gupta, I., Murthy, S.N., Hollenbach, A., and Raj, H.G. 2013. Simultaneous inhibition of cell cycle, proliferation, survival, metastatic pathways and induction of apoptosis in breast cancer cells by a phytochemical super-cocktail: Genes that underpin its mode of action. *Journal of Cancer*. 4(9): 703-715.
- Ozaki, T., and Nakagawara, A. 2011. Role of p53 in cell death and human cancers. *Cancers*. 3(1): 994-1013.
- Pacher, T., Seger, C., Engelmeier, D., Vajrodaya, S., Hofer, O., and Greger, H. 2002. Antifungal stilbenoids from *Stemona collinsae*. *Journal of Natural Products*. 65(6): 820-827.
- Pandey, R.R., Mondal, T., Mohammad, F., Enroth, S., Redrup, L., Komorowski, J., Nagano, T., Mancini-Dinardo, D., and Kanduri, C. 2008. Kcnqlot1 antisense noncoding RNA mediates lineage-specific transcriptional silencing through chromatin-level regulation. *Molecular Cell*. 32(2): 232-246.
- Park, B.K., Zhang, H., Zeng, Q., Dai, J., Keller, E.T., Giordano, Gu, K., Shah, V., Pei, L., Zarbo, R.J., McCauley, L., Shi, S., Chen, S., and Wang, C.Y. 2007. NF- κ B in breast cancer cells promotes osteolytic bone metastasis by inducing osteoclastogenesis via GM-CSF. *Nature Medicine*. 13(1): 62-69.
- Park, E. 2017. Data on the effects of anti-cancer drug of resveratrol in breast cancer cells, MDA-MB-231 cells. 12(2017): 68-71.
- Park, M.H., and Hong, J.T. 2016. Roles of NF- κ B in cancer and inflammatory disease and their therapeutic approaches. *Cells*. 5(2): 1-15.
- Park, M.H., Hong, J.E., Park, E.S., Yoon, H.S., Seo, D.W., Hyun, B.K., Han, S.B., Ham, Y.W., Hwang, B.Y., and Hong, J.T. 2015. Anticancer effect of tectochrysin in colon cancer cell via suppression of NF- κ B activity and enhancement of death receptor expression. *Molecular Cancer*. 14(124): 1-12.
- Parsa, N. 2012. Environmental factors influencing human cancer. *Iranian Journal of Public Health*. 41(11): 1-9.
- Pellegata, N.S., Antoniono, R.J., Redpath, J.L., and Stanbridge, E.J. 1996. DNA damage and p53-mediated cell cycle arrest: a reevaluation. *Proceedings of the National Academy of Sciences of the United States of America*. 93(26): 15209-15214.
- Pereira, S., and Tettamanti, M. 2005. Ahimsa and alternatives-the concept of the 4th R. The CPCSEA in India. *ALTEX*. 22(1): 3-6.
- Perri, F., Pisconti, S., and Scarpato, G.D.V. 2016. P53 mutations and cancer: a tight linkage. *Annals Of Translational Medicine*. 4(24): 522-525.

- Pflaum, J., Schlosser, S., and Muller, M. 2014. p53 family and cellular stress responses in cancer. *Frontiers in Oncology*. 4(285): 1-15.
- Piccolo, M.T., and Crispi, S. 2012. The dual role played by p21 may influence the apoptotic or anti-apoptotic fate in cancer. *Journal of Cancer Research Updates*. 1(2): 189-202.
- Porter, L.A., and Donoghue, D.J. 2003. Cyclin B1 and CDK1: nuclear localization and upstream regulators. *Progress in Cell Cycle Research*. 5: 335-347.
- Powe, D.G., Voss, M.J., Zanker, K.S., Habashy, H.O., Green, A.R., Ellis, I.O., and Entschladen, F. 2010. Beta-blocker drug therapy reduces secondary cancer formation in breast cancer and improves cancer specific survival. *Oncotarget*. 1(7): 628-638.
- Proskuryakov, S.Y., and Gabai, V.L. 2010. Mechanisms of tumor cell necrosis. *Current Pharmaceutical Design*. 16(1): 56-68.
- Qu, Y., Han, B., Yu, Y., Yao, W., Bose, S., Karlan, B.Y., Guiliano, A.E., and Cui, X. 2015. Evaluation of MCF10A as a reliable model for normal human mammary epithelial cells. *PLOS ONE*. 10(7): 1-16.
- Rasmussen, L., and Arvin, A. 1982. Chemotherapy-induced immunosuppression. *Environmental Health Perspectives*. 43: 21-25.
- Rastogi, N., and Mishra, D.P. 2012. Therapeutic targeting of cancer cell cycle using proteasome inhibitors. *Cell Division*. 7(26): 1-10.
- Ray, D., Murphy, K.R., and Gal, S. 2012. The DNA binding and accumulation of p53 from breast cancer cell lines and the link with serine 15 phosphorylation. *Cancer Biology and Therapy*. 13(10): 848-857.
- Reis-Filho, J.S and Tutt, A.N. 2008. Triple negative tumours: a critical review. *Histopathology*. 52 (1): 108-118.
- Rhind, N., and Russell, P. 2012. Signaling pathways that regulate cell division. *Cold Spring Harbor Perspectives in Biology*. 4(10): 1-15.
- Rhodes, L.V., Tate, C.R., Hoang, V.T., Burks, H.E., Gilliam, D., Martin, E.C., Elliot, S., Miller, D.B., Buechlein, A., Rusch, D., Tang, H., Nephew, K.P., Burrow, M.E., and Collins-Burrow, B.M. 2015. Regulation of triple-negative breast cancer cell metastasis by the tumor-suppressor liver kinase B1. *Oncogenesis*. 4: 1-8.
- Ricci, M.S., and Zong, W.X. 2006. Chemotherapeutic approaches for targeting cell death pathways. *Oncologist*. 11(4): 342-357.
- Riedl, S.J., and Salvesen, G.S. 2007. The apoptosome: signalling platform of cell death. *Nature Reviews: Molecular Cell Biology*. 8(5): 405-413.

- Riedl, S.J., and Shi, Y. 2004. Molecular mechanisms of caspase regulation during apoptosis. *Nature Reviews. Molecular Cell Biology*. 5(11): 897-907.
- Robinson, T.J.W., Liu, J.C., Vizeacoumar, F., Sun, T., Maclean, N., Egan, S.E., Schimmer, A.D., and Zacksenhaus, E. 2013. RB1 status in triple negative breast cancer cells dictates response to radiation treatment and selective therapeutic drugs. *PLOS ONE*. 8(11): 1-11.
- Schwartz, G.K., and Shah, M.A. 2005. Targeting the cell cycle: a new approach to cancer therapy. *Journal of Clinical Oncology*. 23(36): 9408-9421.
- Schweichel, J.U., and Merker, H.J. 1973. The morphology of various types of cell death in prenatal tissues. *Teratology*. 7(3): 253-266.
- Sherr, C.J. 2000. The Pezcoller lecture: cancer cell cycles revisited. *Cancer Research*. 60(4): 3689-3695.
- Shi, Y., Yang, S., Troup, S., Lu, X., Callaghan, S., Park, D.S., Xing, Y., and Yang, X. 2011. Resveratrol induces apoptosis in breast cancer cells by E2F1-mediated up-regulation of ASPP1. *Oncology Reports*. 25: 1713-1719.
- Shrivastava, A., Kuzontkoski, P.M., Groopman, J. E., and Prasad, A. 2011. Cannabidiol induces programmed cell death in breast cancer cells by coordinating the cross-talk between apoptosis and autophagy. *Molecular Cancer Therapeutics*. 10(7): 1161-72.
- Siegel, R., Desantis, C., Virgo, K., Stein, K., Mariotto, A., Smith, T., Cooper, D., Gansler, T., Lerro, C., Fedewa, S., Lin, C., Leach, C., Cannady, R.S., Cho, H., Scoppa, S., Hachey, M., Kirch, R., Jemal, A., and Ward, E. 2012. Cancer treatment and survivorship statistics, 2012. *CA: A Cancer Journal for Clinicians*. 62(4): 220-241.
- Sionov, R.V., and Haupt, Y. 1999. The cellular response to p53: the decision between life and death. *Oncogene*. 18(45): 6145-6157.
- Smith, S.M., Lyu, Y.L., and Chai, L. 2014. NF- κ B affects proliferation and invasiveness of breast cancer cells by regulating CD44 Expression. *PLOS ONE*. 9(9): 1-10.
- Soule, H.D., Maloney, T.M., Wolman, S.R., Peterson, W.D.J., Brenz, R., McGrath, C.M., Russo, J., Pauley, R.J., Jones, R.F., and Brooks, S.C. 1990. Isolation and characterization of spontaneously immortalized human breast epithelial cell line, MCF-10A. *Cancer Research*. 50(18): 6075-6086.
- Sprouse, A.A., and Herbert, B.S. 2014. Resveratrol augments paclitaxel treatment in MDA-MB-231 and paclitaxel-resistant in MDA-MB-231 breast cancer cells. *International Journal of Cancer Research and treatment*. 34(10): 5363-5374.

- Su, J., Zhao, P., Kong, L., Li, X., Yan, J., Zheng, Y., and Li, Y. 2013. Trichothecin induces cell death in NF- κ B constitutively activated human cancer cells via inhibition of IKK β phosphorylation. *PLOS ONE*. 8(8): 1-8.
- Sultan, A.S., Khalil, M.I.M., Sami, B.M., Alkhuriji, A.F., and Sadek, O. 2017. Quercetin induces apoptosis in triple-negative breast cancer cells via inhibiting fatty acid synthase and β -catenin. *International Journal of Clinical and Experimental Pathology*. 10(1): 156-172.
- Symington, C.F. 1974. Foresters' Manual of Dipterocarps. University Malaya Publication, Kuala Lumpur. 1-356.
- Takahashi, K., Tanaka, M., Inagaki, A., Wanibuchi, H., Izumi, Y., Miura, K., Nagayama, K., Shiota, M., and Iwao, H. 2013. Establishment of a 5-fluorouracil-resistant triple-negative breast cancer cell line. *International Journal of Oncology*. 43(6): 1985-1991.
- Takaya, Y., Yan, K.X., Terashima, K., Ito, J., and Niwa, M. 2002. Chemical determination of the absolute structures of resveratrol dimers, ampelopsin A, B, D and F. *Tetrahedron*. 58(36): 7259-7265.
- Taraphdar, A.K., Roy, M., and Bhattacharya, R.K. 2001. Natural products as inducers of apoptosis: Implication for cancer therapy and prevention. *Current Science*. 80(11): 1387-1396.
- Taylor, W.R., and Grabovich, A. 2009. Targeting the cell cycle to kill cancer cells. pp 429-453. Academic Press: California.
- Taylor, W.R., and Stark, G.R. 2001. Regulation of G2/M transition by p53. *Oncogene*. 20(15): 1803-1815.
- Thanasoula, M., Escandell, J.M., Suwaki, N., and Tarsounas, M. 2012. ATM/ATR checkpoint activation downregulates CDC25C to prevent mitotic entry with uncapped telomeres. *EMBO Journal*. 31(16): 3398-3410.
- Tsao, Y.P., Huang, S.J., Chang, J.L., Hsieh, J.T., Pong, R.C., and Chen, S.L. 1999. Adenovirus-mediated *p21((WAF1/SDII/CIP1))* gene transfer induces apoptosis of human cervical cancer cell lines. *Journal of Virology*. 73(6): 4983-4990.
- Tseng, T.T., Chien, M.H., Lin, W.L., Wen, Y.C., Chow, J.M., Chen, C.K., Kuo, T.C., and Lee, W.J. 2016. Inhibition of MDA-MB-231 breast cancer cell proliferation and tumor growth by apigenin through induction of G2/M arrest and histone H3 acetylation-mediated p21^{WAF1/CIP1} expression. *Environmental Toxicology*. 32(2): 434-444.
- Tugba, A.F., Karagoz, A., Ozcan, G., Melikoglu, G., Anil, S., Kultur, S., and Sutlupinar, N. 2016. *In vitro* anticancer and cytotoxic activities of some plant extracts on HeLa and Vero cell lines. *Journal of Balkan Union of Oncology*. 21(3): 720-725.

- Turner, N., Moretti, E., Siclari, O., Migliaccio, I., Santarpia, L., D'Incalci, M., Piccolo, S., Veronesi, A., Zambelli, A., Del Sal, G., and Di Leo, A. 2013. Targeting triple negative breast cancer: is p53 the answer? *Cancer Treatments Reviews*. 39(5): 541-550.
- Turner, T. 2012. Development of the Polio Vaccine: A historical perspective of Tuskegee University's role in mass production and distribution of HeLa cells. *Journal of Health Care Poor Underserved*. 23(40): 5-10.
- Ulukaya, E., Acilan, C., and Yilmaz, Y. 2011. Apoptosis: why and how does it occur in biology? *Cell Biochemistry and Function*. 29(6): 468-480.
- Vakkila, J., and Lotze, M.T. 2004. Inflammation and necrosis promote tumor growth. *Nature Reviews Immunology*. 4(8): 641-648.
- Valentini, C.G., Fianchi, L., Voso, M.T., Caira, M., Leone, G., and Pagano, L. 2011. Incidence of acute myleoid leukemia after breast cancer. *Mediterranean Journal of Hematology and Infectious Disease*. 3(1): 1-6.
- Venkatadri, R., Muni, T., Iyer, A.K.V., Yakisich, J.S., and Azad, N. 2016. Role of apoptosis-related miRNAs in resveratrol-induced breast cancer cell death. *Cell Death and Disease*. 7(2): 1-12.
- Verhoven, B., Schlegel, R.A., and Williamson, P. 1995. Mechanisms of phosphatidylserine exposure, a phagocyte recognition signal, on apoptotic T lymphocytes. *Journal of Experimental Medicine*. 182(5): 1597-1601.
- Vogel, C., Kienitz, A., Muller, R., and Bastians, H. 2005. The mitotic spindle checkpoint is a critical determinant for topoisomerase-based chemotherapy. *Journal of Biological Chemistry*. 280(6): 4025-4028.
- Vousden, K.H., and Prives, C. 2009. Blinded by the light: the growing complexity of p53. *Cell*. 137(3): 413-431.
- Walerych, D., Napoli, M., Collavin, L., and Sal, G.D. 2012. The rebel angel: mutant p53 as the driving oncogene in breast cancer. *Carcinogenesis*. 33(11): 2007-2017.
- Walsby, E., Pearce, L., Burnett, A.K., Fegan, C., and Pepper, C. 2012. The Hsp90 inhibitor NVP-AUY922-AG inhibits NF- κ B signaling, overcomes microenvironmental cytoprotection and is highly synergistic with fludarabine in primary CLL cells. *Oncotarget*. 3(5): 525-534.
- Wang, D.J., Ratnam, N.M., Byrd, J.C., and Guttridge, D.C. 2014a. NF- κ B functions in tumor initiation by suppressing the surveillance of both innate and adaptive immune cells. *Cell Reports*. 9: 90-103.
- Wang, F., Gao, Y., and Gao, L. 2011. Study on the electrochemical behaviour of the anticancer herbal drug berberine and its analytical application. *Journal of the Chinese Chemical Society*. 58(4): 450-456.

- Wang, W., Zhang, L., Chen, T., Guo, W., Bao, X., Wang, D., Ren, B., Wang, H., Li, Y., Wang, Y., Chen, S., Tang, B., Yang, Q., and Chan, C. 2017. Anticancer effects of resveratrol-loaded solid lipid nanoparticles on human breast cancer cells. *Molecules*. 22(1814): 1-11.
- Wang, Z., Fan, M., Candas, D., Zhang, T.Q., Qin, L., Eldridge, A., Sebastian, W.H., Kazi, M.A., Brett, A.C., Nantajit, D., Duru, N., He, F., Chen, M., Finkel, T., Weinstein, L.S., and Li, J.J. 2014b. Cyclin B1/cdk1 coordinates mitochondrial respiration for cell-cycle G₂/M progression. *Developmental Cell*. 29(2): 217-232.
- Wesierska-Gadek, J., Schreiner, T., Maurer, M., Waringer, A., and Ranftler, C. 2007. Phenol red in the culture medium strongly affects the susceptibility of human MCF-7 cells to roscovitine. *Cellular and Molecular Biology Letters*. 12(2): 280-293.
- Wibowo, A., Ahmat, N., and Hamzah, A. 2011a. Oligostilbenoids from the stem bark of *Dryobalanops aromatica*. *Planta Medica*. 77(12): 9-10.
- Wibowo, A., Ahmat, N., Hamzah, A.S., Ismail, N.H., Ahmad, R., and Jaafar, F.M. 2012a. Resveratrol oligomers from the stem bark of *Dryobalanops aromatica*. *Biochemical Systematics and Ecology*. 40: 62-64.
- Wibowo, A., Ahmat N., Hamzah A.S., Latif, F.A., Norrizah, J.S., Khong, H.Y., and Takayama, H. 2014. Identification and biological activity of secondary metabolites from *Dryobalanops beccarii*. *Phytochemistry Letter*. 9: 117-122.
- Wibowo, A., Ahmat, N., Hamzah, A.S., Low, A.L.M., Mohamad, S.A.S., Khong, H.Y., Sufian, A.S., Manshoor, N., and Takayama, H. 2012b. Malaysianol B, an oligostilbenoid derivative from *Dryobalanops lanceolata*. *Fitoterapia*. 83: 1569-1575.
- Wibowo, A., Ahmat, N., Hamzah, A.S., Sufian, A.S., Ismail, N.H., Ahmad, R., Jaafar, F.M., and Takayama, H. 2011b. Malaysianol A, a new trimer resveratrol oligomer from the stem bark of *Dryobalanops aromatica*. *Fitoterapia*. 82(4): 676-681.
- Wibowo, A., and Ahmat, N. 2015. Chemotaxonomic significance of olistilbenoids isolated from *Dryobalanops* in the taxonomic of Dipterocarpaceae. *Biochemical Systematics and Ecology*. 59: 31-35.
- Williams, G.H., and Stoeber, K. 2012. The cell cycle and cancer. *Journal of Pathology*. 226: 352-364.
- Winter, E., Chiaradia, L.D., Silva, A.H., Nunes, R.J., Yunes, R.A., and Creczynski-Pasa, T.B. 2014. Involvement of extrinsic and intrinsic apoptotic pathways together with endoplasmic reticulum stress in cell death induced by naphthylchalcones in a leukemic cell line: Advantages of multi-target action. *Toxicology In Vitro*. 28(5): 769-777.

- Wong, R.S.Y. 2011. Apoptosis in cancer: from pathogenesis to treatment. *Journal of Experimental and Clinical Cancer Research*. 30(1): 87-101.
- Xia, M., Knezevic, D., and Vassilev, L.T. 2011. p21 does not protect cancer cells from apoptosis induced by nongenotoxic p53 activation. *Oncogene*. 30(3): 346-355.
- Xia, Y., Shen, S., and Verma, I.M. 2014. NF- κ B, an active player in human cancers. *Cancer Immunology Research*. 2(9): 823-830.
- Xiao, X., Yang, G., Bai, P., Gui, S., Nyuyen, T.M.B., Mercado-Urbe, I., Yang, M., Zou, J., Li, Q., Xiao, J., Chang, B., Liu, G., Wang, H., and Liu, J. 2016. Inhibition of nuclear factor-kappa B enhances the tumor growth of ovarian cancer cell line derived from a low-grade papillary serous carcinoma in p53-independent pathway. *BioMed Central Cancer*. 16(582): 1-13.
- Xu, L., Lao, Y., Zhao, Y., Qin, J., Fu, W., Zhang, Y., and Xu, H. 2015. Screening active compounds from *Garcinia* species native to China reveals novel compounds targeting the STAT/JAK signaling pathway. *BioMed Research International*. 2015: 1-10.
- Xu, S.Q., and El-Deiry, W.S. 2000. p21(WAF1/CIP1) inhibits initiator caspase cleavage by TRAIL death receptor DR4. *Biochemical and Biophysical Research Communications*. 269(1): 179-190.
- Xue, Y.Q., Di, J.M., Luo, Y., Cheng, K.J., Wei, X., and Shi, Z. 2014. Resveratrol oligomers for the prevention and treatment of cancers. *Oxidative Medicine and Cellular Longevity*. 2014: 1-9.
- Yam, C.H., Fung, T.K., and Poon, R.Y. 2002. Cyclin A in cell cycle control and cancer. *Cellular and Molecular Life Sciences*. 59(8): 1317-1326.
- Yamada, M., Hayashi, K.I., Hayashi, H., Tsuji, R., Kakumoto, K., Ikeda, S., Hoshino, T., Tsutsui, K., Ito, T., Iinuma, M., and Nozaki, H. 2006. Nepalensinols D-G new resveratrol oligomers from *Kobresia hepalensis* (Cyperaceae) as potent inhibitors of DNA-topoisomerase II. *Chemical and Pharmaceutical Bulletin*. 54(3): 354-358.
- Yang, X.R., Chang-Claude, J., Goode, E.L., Couch, F.J., Nevanlinna, H., Milne, R.L., Gaudet, M., Schmidt, M.K., Brooks, A., Cox, A., Fasching, P.A., Hein, R., Spurdle, A.B., Blows, F., Driver, K., Flesch-Janys, D., Heinz, J., Sinn, P., Vrieling, A., Heikkinen, T., Aittomäki, K., Heikkilä, P., Blomqvist, C., Lissowska, J., Peplonska, B., Chanock, S., Figueroa, J., Brinton, L., Hall, P., Czene, K., Humphreys, K., Darabi, H., Liu, J., Van 't Veer, L.J., van Leeuwen, F.E., Andrulis, I.L., Glendon, G., Knight, J.A., Mulligan, A.M., O'Malley, F.P., Weerasooriya, N., John, E.M., Beckmann, M.W., Hartmann, A., Weihbrecht, S.B., Wachter, D.L., Jud, S.M., Loehberg, C.R., Baglietto, L., English, D.R., Giles, G.G., McLean, C.A., Severi, G., Lambrechts, D., Vandrope, T., Weltens, C., Paridaens, R., Smeets, A., Neven, P., Wildiers, H., Wang, X., Olson, J.E., Cafourek, V., Fredericksen, Z., Kosel, M., Vachon, C., Cramp, H.E., Connley, D., Cross, S.S., Balasubramanian, S.P., Reed, M.W., Dörk, T., Bremer, M.,

- Meyer, A., Karstens, J.H., Ay, A., Park-Simon, T.W., Hillemanns, P., Arias Pérez, J.I., Menéndez Rodríguez, P., Zamora, P., Benítez, J., Ko, Y.D., Fischer, H.P., Hamann, U., Pesch, B., Brüning, T., Justenhoven, C., Brauch, H., Eccles, D.M., Tapper, W.J., Gerty, S.M., Sawyer, E.J., Tomlinson, I.P., Jones, A., Kerin, M., Miller, N., McInerney, N., Anton-Culver, H., Ziogas, A., Shen, C.Y., Hsiung, C.N., Wu, P.E., Yang, S.L., Yu, J.C., Chen, S.T., Hsu, G.C., Haiman, C.A., Henderson, B.E., Le Marchand, L., Kolonel, L.N., Lindblom, A., Margolin, S., Jakubowska, A., Lubiński, J., Huzarski, T., Byrski, T., Górski, B., Gronwald, J., Hoening, M.J., Hollestelle, A., van den Ouweland, A.M., Jager, A., Kriege, M., Tilanus-Linthorst, M.M., Collée, M., Wang-Gohrke, S., Pylkäs, K., Jukkola-Vuorinen, A., Mononen, K., Grip, M., Hirvikoski, P., Winqvist, R., Mannermaa, A., Kosma, V.M., Kauppinen, J., Kataja, V., Auvinen, P., Soini, Y., Sironen, R., Bojesen, S.E., Ørsted, D.D., Kaur-Knudsen, D., Flyger, H., Nordestgaard, B.G., Holland, H., Chenevix-Trench, G., Manoukian, S., Barile, M., Radice, P., Hankinson, S.E., Hunter, D.J., Tamimi, R., Sangrajrang, S., Brennan, P., McKay, J., Odefrey, F., Gaborieau, V., Devilee, P., Huijts, P.E., Tollenaar, R.A., Seynaeve, C., Dite, G.S., Apicella, C., Hopper, J.L., Hammet, F., Tsimiklis, H., Smith, L.D., Southey, M.C., Humphreys, M.K., Easton, D., Pharoah, P., Sherman, M.E., and Clossas, M.G. 2011. Association of breast cancer risk factors with tumor subtypes: a pooled analysis from the breast cancer association consortium studies. *Journal of the National Cancer Institute*. 103(3): 250-263.
- Yardley, D.A. 2013. Drug resistance and the role of combination chemotherapy in improving patients outcomes. *International Journal of Breast Cancer*. 2013: 1-15.
- Yu, H.J., Jung, J.Y., Jeong, J.H., Cho, S.D., and Lee, J.S. 2015. Induction of apoptosis by parthenolide in human oral cancer cell lines and tumor xenografts. *Oral Oncology*. 51(6): 602-609.
- Zaffaroni, N., Marco, C.D., Villa, R., Riboldi, S., Daidone, M.G., and Double, J.A. 2001. Cell growth inhibition, G₂M cell cycle arrest and apoptosis induced by the imidazoacridinone C1311 in human tumour cell lines. *European Journal of Cancer*. 37(15): 1953-1962.
- Zain, W.Z.W.M., and Jusoff, K. 2010. Laevifonol: A unique dimer oligostilbene from the stem bark of *Vatica orodata*. *World Applied Sciences Journal*. 8(9): 1056-1059.
- Zasshi, Y. 2011. Structures of oligostilbenoids in Dipterocarpaceous plants and their biological activities. *Pharmaceutical Society of Japan*. 131(1): 93-100.
- Zhou, Q., Wang, S., Zhang, H., Lu, Y., Wang, X., Motoo, Y., and Su, S. 2009. The combination of baicalin and baicalein enhances apoptosis via the ERK/p38 MAPK pathway in human breast cancer cells. *Acta Pharmacologica Sinica*. 30(12): 1648-1658.
- Zong, W.X., and Thompson, C.B. 2006. Necrotic death as a cell fate. *Genes and Development*. 20(1): 1-15.