UNIVERSITI PUTRA MALAYSIA

CYTOTOXICITY AND MODE OF ACTION OF Barrientosiimonas humi EXTRACT AGAINST BREAST CANCER CELL LINES

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By

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Thesis submitted to the School of Graduate Studies, Universiti Putra Malaysia, in fullfillment of the requirements for the Degree of Doctor of Philosophy

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CYTOTOXICITY AND MODE OF ACTION OF *Barrientosiimonas humi* EXTRACT AGAINST BREAST CANCER CELL LINES

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March 2021

Chair : Professor Cheah Yoke Kqueen, PhD
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Secondary metabolites from novel extremophilic actinobacteria are found to be potent sources of diverse novel anti-cancer compounds. Currently, development of new and effective cancer therapies remains a challenge due to the problems of systemic toxicity and multidrug resistance in cancer. *Barrientosiimonas humi* is a novel soil actinobacteria, which was isolated from Barrientos Island, Antarctica. The genus *Barrientosiimonas* belongs to the order Actinomycetales, which have ability in producing diverse pharmacological compounds. In this study, the cytotoxic effects of ethyl acetate extract and compounds isolated from *B. humi* were examined using bioassay-guided fractionation, and the molecular pathway involved was also determined. The ethyl acetate extract was obtained from fermentation of *B. humi* by using solvent extraction and fractionation of the crude extract was conducted via column chromatography. Cytotoxicity was evaluated by using MTT and the iCELLigence Real-Time Cellular Analysis (RTCA) assays. Morphological changes, cell death mechanism, cell cycle profiles and caspases expressions of treated breast cancer cells (MCF-7 and MDA-MB-231) were determined. Furthermore, metabolic alterations induced by *B. humi* on MDA-MB-231 cells were assessed by Biolog's Phenotype (PM-M) MicroArray. Major compounds present in *B. humi* were isolated using different chromatographic techniques. Results revealed that ethyl acetate extract isolated from *B. humi* (EA-BH) was cytotoxic against both MCF-7 and MDA-MB-231 cells. The extract was then subjected to bioassay-guided fractionation, which yielded four fractions. One of the purified fractions, designated as DCM-F2, exhibited the strongest cytotoxic activity among all the fractions and thereby was selected for further studies. DCM-F2 had selective cytotoxic effect on MCF-7 and MDA-MB-231 cells in concentration- and time-dependent manners. DCM-F2 inhibited cell growth by induction of apoptosis cell death and cell cycle arrest. DCM-F2 triggered apoptosis cell death in both MCF-7 and MDA-MB-231 cells, particularly in the early stage apoptosis. The caspase-3/7 activity in DCM-F2 treated MDA-MB-231 cells showed caspase-dependent apoptosis, whereas MCF-7 showed caspase-independent apoptosis. Based on the cell cycle profile, cells treated with DCM-F2 caused significant inhibition of

cell cycle progression at 72 h and leading to an increase in the G0/G1 population. PM-M assay analysis revealed that the most associated metabolic pathway following treatment of MDA-MB-231 cells with DCM-F2 was glycolysis metabolism. A total of five compounds were successfully obtained. Diketopiperazine, (-)-cyclo (Pro-Tyr) was demonstrated to be the most cytotoxic and selective against MCF-7 and MDA-MB-231 cells compared to other compounds. As a conclusion, EA-BH exhibits significant cytotoxicity in MCF-7 and MDA-MB-231 cells with low toxicity by inducing apoptotic-related pathways, cell cycle arrest and altered glycolytic pathway. These results highlight the potential therapeutic value of *B. humi* in breast cancer treatment.

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

SITOTOKSIK DAN MOD TINDAKAN *Barrientosiimonas humi* EKSTRAK TERHADAP SEL KANSER PAYUDARA

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Metabolit sekunder dari aktinobakteria ekstremofilik baru mempunyai potensi tinggi dalam menghasilkan pelbagai sebatian antikanser baru. Pada masa ini, pembangunan terapi kanser yang baru dan berkesan menjadi cabaran kerana masalah keracunan sistemik dan rintangan ubat-ubatan dalam kanser. *Barrientosiimonas humi* adalah aktinobakteria baru yang diasingkan dari sampel tanah yang dikutip dari Pulau Barrientos, Antartika. Genus *Barrientosiimonas* yang berasal dari order Actinomycetales boleh menghasilkan pelbagai sebatian farmakologi. Dalam kajian ini, kesan sitotoksik ekstrak etil asetat dan sebatian yang diasingkan dari *B. humi* diuji menggunakan fraksionasi berpandukan bioasai, dan laluan molekul yang terlibat telah ditentukan. Ekstrak etil asetat diperoleh daripada penapaian *B. humi* dengan menggunakan ekstraksi pelarut. Pemencilan ekstrak mentah dilakukan melalui kromatografi lajur. Sitotoksik ditentukan dengan menggunakan ujian MTT dan Analisis Masa Selular (RTCA). Perubahan morfologi, mod kematian sel, profil kitar sel dan ekspresi caspases sel-sel kanser payudara (MCF-7 dan MDA-MB-231) telah ditentukan. Tambahan pula, perubahan metabolik yang diakibatkan oleh *B. humi* pada sel MDA-MB-231 telah dinilai menggunakan Biolog's Phenotype Microarray (PM). Sebatian utama yang terdapat dalam *B. humi* terpencil menggunakan teknik kromatografi yang berbeza. Keputusan menunjukkan bahawa ekstrak etil asetat yang diasingkan dari *B. humi* (EA-BH) adalah sitotoksik terhadap kedua-dua sel MCF-7 dan MDA-MB-231. Ekstrak ini kemudiannya tertakluk kepada pemencilan berpandukan bioasai, yang menghasilkan empat pecahan. Salah satu pecahan, yang ditetapkan sebagai DCM-F2, menunjukkan aktiviti sitotoksik yang paling kuat di antara semua pecahan dan dengan itu dipilih untuk kajian selanjutnya. DCM-F2 mempunyai kesan sitotoksik terpilih pada sel-sel MCF-7 dan MDA-MB-231 bergantung pada masa dan dos. DCM-F2 menghalang pertumbuhan sel dengan induksi apoptosis dan penangkapan kitaran sel. DCM-F2 menyebabkan apoptosis dalam kedua-dua sel, terutamanya pada peringkat awal apoptosis. Aktiviti caspase-3/7 di DCM-F2 yang dirawat MDA-MB-231 sel menunjukkan apoptosis yang bergantung kepada caspase, sedangkan MCF-7 menunjukkan apoptosis bebas caspase. Berdasarkan profil kitaran

sel, DCM-F2 menyebabkan perencatan besar perkembangan kitaran sel pada 72 jam dengan peningkatan populasi G0/G1. Analisis asai PM-M menunjukkan bahawa laluan metabolik yang paling berkaitan selepas mendedahkan MDA-MB-231 sel ke DCM-F2 adalah metabolisme glikolisis. Sebanyak lima sebatian telah berjaya diasingkan. Diketopiperazin, (-)-siklo (-Pro-Tir), adalah sebatian yang paling sitotoksik dan selektif kepada kanser payudara berbanding dengan sebatian lain. Kesimpulannya, EA-BH menunjukkan sitotoksisiti yang ketara pada sel MCF-7 dan MDA-MB-231 dengan ketoksikan yang rendah melalui jalur apoptotik, penahanan kitaran sel dan perubahan jalur glikolitik. Hasil ini menunjukkan nilai terapi *B. humi* yang berpotensi dalam rawatan kanser payudara.

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

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Acetyl-CoA	Acetyl coenzyme A
AIF	Apoptosis-inducing factor
ANOVA	One-way analysis of variance
ATCC	American Type Culture Collection
ATP	Adenosine triphosphate
BECN1	Beclin 1
BuOH	n-Butanol
CDK	Cyclin-dependent kinases
$CHCl_3$	Chloroform
COSY	^{1}H- ^{1}H Correlation Spectroscopy
dATP	Deoxyadenosine triphosphate
DCM	Dichloromethane
dH_2O	Distilled water
DKP	Diketopiperazines
DMEM	Dulbecco's modified eagle medium
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
EDTA	Trypsin-ethylenediaminetetraacetics acid
ER	Estrogen receptor
ESIMS	Electrospray ionization mass spectrometry
EtOAc	Ethyl acetate
EtOH	Ethanol
$FADH_2$	Flavin adenine dinucleotide
FAS	Cell surface death receptor

FBS	Fetal bovine serum
FDA	The Food and Drug Administration
FKBP12	FK506-binding protein 12
FT-IR	Fourier-transform infrared spectroscopy
GLUT1	Glucose transporter 1
H_2SO_4	Sulphuric acid
HER2	Human epidermal growth factor receptor 2
HIF-1α	Hypoxia inducible factor- 1α
HMBC	Heteronuclear Multiple Bond Correlation
HMQC	Heteronuclear multiple quantum coherence
IAPs	Inhibitors of apoptosis proteins
IC_{50}	Half maximal inhibitory concentration
LC-MS	Liquid chromatography–mass spectrometry
LDH	Lactate dehydrogenase
MDR	Multidrug resistance
MEM	Minimum essential medium
MeOH	Methanol
MHz	Megahertz
mTOR	The mammalian target of rapamycin
MTT	3-(4,5- dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
NADH	Nicotinamide adenine dinucleotide
NaOH	Sodium hydroxide
NaP	Sodium-pyruvate
NMR	Nuclear magnetic resonance
Ox-Phos	Oxidative phosphorylation

p21/Cip1	Cyclin-dependent kinase inhibitor 1
p53	Tumour suppressor gene
PBS	Phosphate buffer saline
PCD	Programmed cell death
PKA	Protein Kinase A
PKC	Protein kinase C
PM	Phenotype Microarray
PM-M	Phenotype Microarray for Mammalian Cells
PS	Phosphatidylserine
RC	Radial chromatography
RIP	Receptor-interacting protein kinases
RNA	Ribonucleic acid
RT	Room temperature
RTCA	Real Time Cell Analysis
SD	Standard deviation
SI	Selectivity index
TCA	Tricarboxylic acid
TLC	Thin Layer Chromatography
TNBC	Triple-negative breast cancers
TNFα	Tumour necrosis factor-α
TRAIL	TNF related apoptosis inducing ligand
TXNIP	Thioredoxin-interacting protein
WHO	World Health Organization
XIAP	X-linked inhibitor of apoptosis protein
^{13}C NMR	Carbon nuclear magnetic resonance

^{1}H NMR	Proton nuclear magnetic resonance
7-AAD	7-amino-actinomycin D

CHAPTER 1

INTRODUCTION

Cancer is the leading cause of morbidity and mortality worldwide, where the incidence rate of cancer cases appears to be on the rise in recent years (Sung *et al*., 2021). The global emergence of multidrug-resistant in cancer causes enormous healthcare costs. Many chemotherapeutic drugs available in the market cause adverse effects in patients with reduced therapeutic effect. Also, treatment of cancer is complex and challenging because numerous biochemical pathways are involved. To date, the development of new anti-cancer agents, preferably natural products with novel mode of action/ mechanisms, is an urgent medical need. About 83% of the approved anti-cancer drugs are isolated from natural origins as they are considered less toxic and safer than synthetic drugs (Newman and Gragg, 2016).

Actinobacteria are the most promising producers for medically important secondary metabolites with diverse biological activities including antimicrobial, antioxidant, antitumour and antiviral activities (Manivasagan *et al*., 2014). Actinobacteria isolated from soil, in particular, have been found to be important for the discovery of diverse commercially available anti-cancer drugs, such as doxorubicin, bleomycin and mitomycin (Pettit, 2004). Isolation and identification of novel actinobacteria is of great interest for the discovery of new and novel therapeutic drugs because this genus could produce compounds with highly active secondary metabolites with low toxicity. However, nowadays, it has become an increasingly daunting challenge to search for suitable drug leads from microbial sources, due to frequent genetic exchange among microorganisms that may share similar physical and chemical features to survive in a specific environment (Bredholt *et al*., 2008).

Current trend has been shifted to the isolation of actinobacteria from exotic and less explored sites such as marine (Manivasagan *et al*., 2014), and polar regions (Ivanova *et al*., 2007). Various extremophilic actinobacteria are able to survive under hostile habitat due to their diverse physiology, metabolic adaptability and flexibility. Thus, there is a high possibility that the extremophilic actinobacteria could produce new valuable metabolites. Previously, more than 50 rare actinobacteria have been identified, which are known to produce more than 2500 active compounds (Kurtboke, 2012).

Barrientosiimonas humi (*B. humi*) is a novel extremophilic soil actinobacteria isolated from Barrientos Island, Antarctica in 2007. It belongs to the members of family *Dermacoccaceae* under phylum actinobacteria (Lee *et al.*, 2013). The preliminary screening of crude extract from *B. humi* exhibited a broad spectrum of antibacterial and anti-cancer activities on HT-29 colon cancer cells (Lee, 2015). This actinobacteria is worth studying because, at present, there is no published report with respect to biological activities of the compounds derived from *B. humi*.

As the continuous study, the present study was conducted to evaluate the cytotoxic activities of the compounds produced by *B. humi* through bioassay-guided fractionation. The bioactive compounds were then isolated for structural elucidation, followed by mode of cell death and metabolomics studies. Identification of effective therapeutic targets which could specifically modulate cell cycle, inhibit cancer cells growth and subsequently activate apoptosis is utmost important. Furthermore, high-throughput metabolic profiling was conducted to determine which metabolic modulations are specific to growth and inhibition of triple-negative breast cancer, by comparing the metabolic profiles of untreated control and treated MDA-MB-231 cells. Assessment of the metabolic alterations induced by bioactive compounds would be a rational approach to discover novel cancer therapeutics.

1.1 Problem statement

Breast cancer was one of the top commonly diagnosed cancers worldwide, contributing 11.7% of all cancer cases diagnosed in 2020. It ranks the top in women for both incidence and mortality rate worldwide with nearly 2.3 million new cases in 2020 (Sung *et al.*, 2018). Due to this alarming statistics, breast cancer become a major public health burden worldwide. Chemotherapy is widely used in breast cancer treatment. Unfortunately, the mortality rate of breast cancer patients is still remains high due to the risk of cancer recurrence and metastasis. The majority of recurrent and metastatic cancer are caused by the development of drug resistance during chemotherapy (Gillet and Gottesman, 2010). Furthermore, chemotherapeutic drugs are prone to cause adverse drug reactions (ADRs) to patients, as most of them are non-selective towards cancer cells, inevitably affect the surrounding normal cells and vital organs like heart, kidney and liver normal cells (Saini *et al*., 2015). Common chemotherapeutic drugs used to treat breast cancer, such as doxorubicin, trastuzumab, cisplatin, paclitaxel, docetaxel and 5-fluorouracil (Lindley and Michaud, 2005) have been reported to cause cardiotoxicity (Volkova and Russell, 2011), hematotoxicity (Goekkurt *et al*., 2009) and hepatotoxicity (Waseem *et al*., 2015). It is clear that current treatment for breast cancer are not ideal due to toxicity, and thus, new kind of chemotherapeutic drugs with better efficacy and minimal side effects are required. Besides that, advances in MDA-MB-231 triple negative breast cancer (TNBC) early diagnostics and therapy are often hindered by the metabolic heterogeneity of the diseases. Although extensive molecular studies have been performed to identify promising therapeutic targets for the identification of TNBC, the metabolomics alterations that indicate the progression of TNBC still remain poorly understood. Therefore, metabolic profiling of the metabolism of TNBC is of clinical importance to improve breast cancer therapeutics.

1.2 Justification for the study

In an attempt to overcome the complications related to current cancer treatment, natural products, produced by certain microorganisms, could be potent lead compounds with good cytotoxicity against cancer cells with lower systemic toxicity. Currently, isolation of new actinobacteria from poorly explored regions such as polar region has caught the attention of researchers. Previous studies revealed that

compounds derived from extremophilic actinobacteria has anti-cancer properties (Shivlata and Satyanarayana, 2015; Abdel-Mageed *et al.*, 2010; Berdy, 2005). In this study, a novel extremophilic actinobacteria, *B. humi* was screened for initial identification of anti-cancer agent because this novel genus actinobacteria belongs to the order Actinomycetales, which have the ability in producing diverse bioactive compounds (Lee *et al*., 2013; Berdy, 2005). In addition, the ethyl acetate extract of *B. humi* was reported to be cytotoxic against HT-29 colon cancer cell line (Lee, 2015). Therefore, it is advantageous to isolate compounds from *B. humi* as a novel bioactive compound could be produced by this novel genus with strong cytotoxicity and selectivity against breast cancer. This actinobacteria is worth studying because, at present, there is no published report with respect to biological activities of the compounds derived from *B. humi* on cancer. Elucidation of a series of molecular events of programmed cell death and metabolic alterations induced by bioactive compounds of *B. humi* in breast cancer cells may lead to the discovery of novel therapeutic targets for anti-cancer drug development.

1.3 Hypothesis

It was hypothesized that ethyl acetate extract of *B. humi* will show cytotoxic effects, activate cell cycle arrest and apoptosis in MCF-7 and MDA-MB-231. The metabolic alterations induced by *B. humi* on MDA-MB-231 will be determined. Subsequently, major compounds present in *B. humi* will be successfully isolated and identified.

1.4 Aims of the study

The general objective of this study was to elucidate the cytotoxicity effect of the secondary metabolites produced by a novel actinobacteria, *Barrientosiimonas humi* (*B. humi*) and the mode of cell death involved in MCF-7 and MDA-MB-231 breast cancer cells.

The specific objectives of this study include:

1. To evaluate cytotoxic effects of *B. humi* crude extract on different cancer cell lines (MCF-7, MDA-MB-231, A549, SCC-9 and HepG2).
2. To examine bioassay-guided fractionation of compounds from ethyl acetate extract of *B. humi* against MCF-7 and MDA-MB-231 cells.
3. To elucidate the mechanism underlying the cytotoxicity of MCF-7 and MDA-MB-231 cells.
4. To assess the metabolic alterations induced by *B. humi* on MDA-MB-231 cells using metabolomics approach.
5. To evaluate cytotoxic effects of the major compounds present in *B. humi* on MCF-7 and MDA-MB-231.

1.5 Conceptual framework

The conceptual framework of research is presented in Figure 1.1. Initially, the crude extract of *B. humi* was prepared and screened via *in vitro* studies. Initial screening results from a previous study showed the crude extract of *B. humi* exhibited significant antibacterial and anti-cancer activities (Lee, 2015). Thus, the cytotoxic effect of the crude extract was further evaluated on different cancer cell lines. The bioactive fractions derived from the crude EtOAc extract were identified based on bioassay-guided fractionation using an optimized organic solvent system. Finally, pure compounds were successfully isolated, moleculer structures of *B. humi* compounds were elucidated. Target compounds were then tested *in vitro* for anti-cancer properties, followed by determination of mechanisms of actions underlying the cytotoxicity.

There are some research directions worth explorations in future studies. For instance, the synergistic effect of the isolated compounds should be further studied to enhance drug efficacy. The signaling pathways induced by bioactive compounds must be examined to unveil its potential as an anti-cancer agent. Also, the complexity of drug discovery process in living organisms such as absorption, distribution, metabolism, and elimination (ADME), metabolism-related pathways (CYP450) should be assessed both *in vitro* and *in vivo*. Cytotoxicity assessment should be carried out using *in vivo* animal model in order to provide true picture on the effectiveness of the isolated compounds. Furthermore, *in silico* computer modelling can be used to predict pharmacokinetic and pharmacodynamics properties before *in vivo* studies.

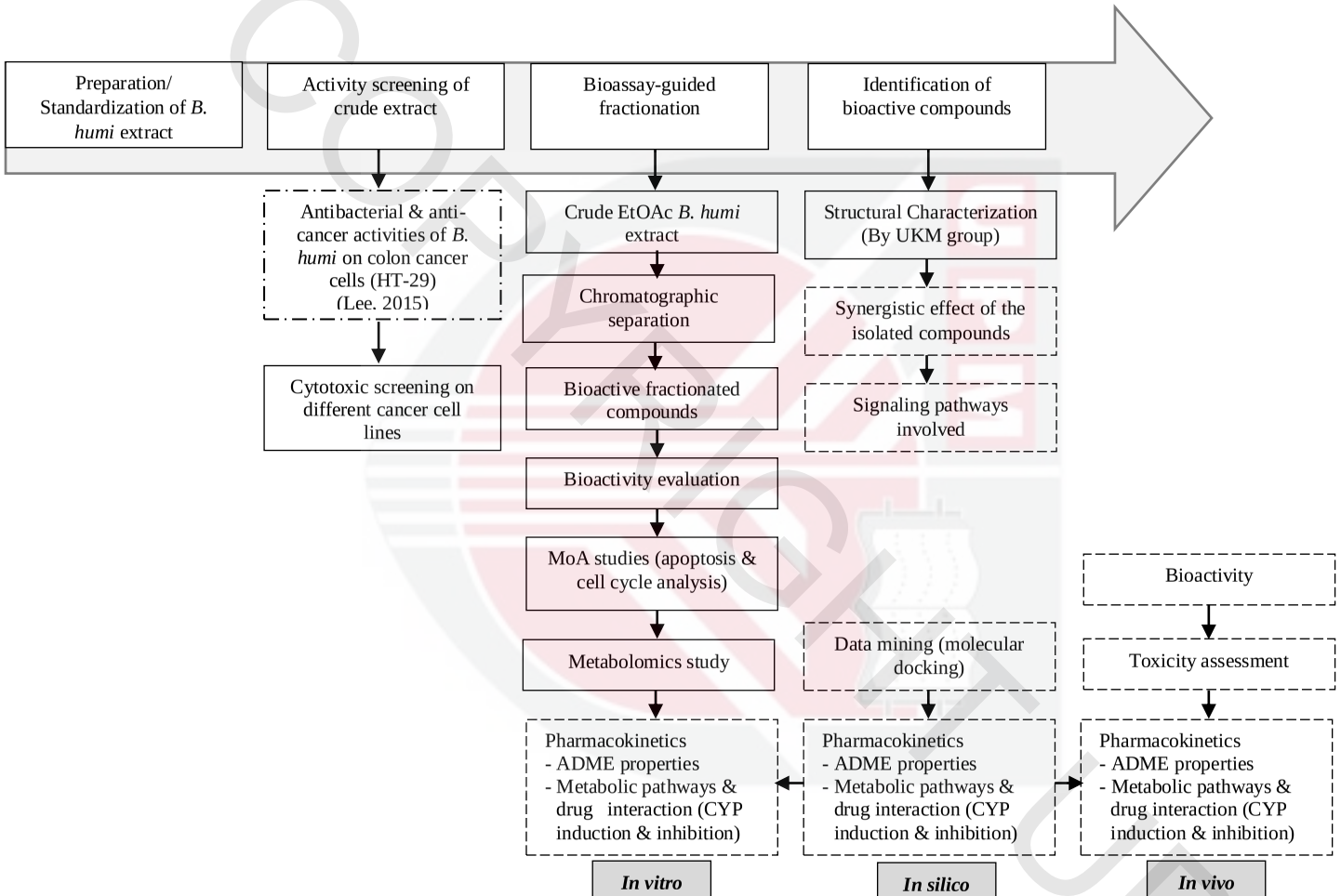

Figure 1.1: Conceptual Framework. The standardized crude extract from a novel actinobacteria (*B. humi*) was screened via *in vitro* system in this study. Line_._._ represented experiment done from previous study; Line___ represented future studies.

REFERENCES

Abdel-Mageed, W. M., Milne, B. F., Wagner, M., Schumacher, M., Sandor, P., Pathomaree, W., Goodfellow, M., Bull, A. T., Horikoshi, K., Ebel, R., Diederich, M., Fiedler, H. P. and Jaspars, M. (2010). Dermacozines, a new phenazine family from deep-sea dermacocci isolated from a Mariana Trench sediment. *Org. Biomolecular Chem.* 8: 2352-2362.

Abdullah, A. H., Mohammed, A. S., Abdullah, R., Mirghani, M. E. S. and Al-Qubaisi, M. (2014). Cytotoxic effects of *Mangifera indica* L. kernel extract on human breast cancer (MCF-7 and MDA-MB-231 cell lines) and bioactive constituents in the crude extract. *BMC Complem. Altern. M.* 14: 199.

Abdullah, N. A., Rozita, W., Mahiyuddin, W., Muhammad, N. A., Ali, Z. M., Ibrahim, L., Saleha, N., Tamim, I., Mustafa, N. and Kamaluddin, M. A. (2013). Survival rate of breast cancer patients in Malaysia: a population-based study. *Asian Pac. J. Cancer Prev.* 14: 4591-4594.

ACS (2017). *Breast cancer facts & figures 2017-2018*. Atlanta: American Cancer Society, Inc.

ACS (2018). Breast cancer. Available: ttps://www.cancer.org/cancer/breastcancer/treatment/targeted-therapy-for-breast cancer.html [Retrieved 9th February, 2019].

Adegboye, M. F. and Babalola, O. O. (2013). Actinomycetes: a yet in exhaustive source of bioactive secondary metabolites. In *Microbial Pathogens and Strategies for Combating Them: Science, Technology and Education*, ed. A. Méndez-Vilas, pp. 786-795. Extremadura: Formatex.

Akash, M. S. H. and Rehman, K. (2020). Column Chromatography. In *Essentials of Pharmaceutical Analysis*, pp. 167-174. Singapore: Springer.

Al-Dhabaan, F. A. M. and Bakhali, A. H. (2017). Analysis of the bacterial strains using Biolog plates in the contaminated soil from Riyadh community. *Saudi J. Biol. Sci*. 24: 901-906.

Anandan, R., Dharumadurai, D. and Manogaran, G. P. (2016). An introduction to actinobacteria. In *Actinobacteria-Basics and Biotechnological Applications*, ed. D. Dhanasekaran, and Y. Jiang, pp. 1-36. London: InTechOpen.

Anderson, K. N., Schwab, R. B. and Martinez, M. E. (2014). Reproductive risk factors and breast cancer subtypes: a review of the literature. *Breast Cancer Res. Treat.* 144: 1-10.

Anderson, N. M., Mucka, P., Kern, J. G. and Feng, H. (2018). The emerging role and target ability of the TCA cycle in cancer metabolism. *Protein Cell* 9: 216-237.

Arcamone, F., Penco, S., Vigevani, A., Redaelli, S., Franchi, G., Dimarco, A., Casazza, A. M., Dasdia, T., Formelli, F., Necco, A. and Soranzo, C. (1975). Synthesis and antitumour properties of new glycosides of daunomycinone and adriamycinone. *J. Med. Chem.* 18: 703-707.

Asai, N., Ohkuni, Y., Kaneko, N., Yamaguchi, E. and Kubo, A. (2014). Relapsed small cell lung cancer: treatment options and latest developments. *Ther. Adv. Med. Oncol.* 6: 69-82.

ASCO (2018). Breast cancer: types of treatment. Available: https://www.cancer.net/cancer-types/breast-cancer/types-treatment [Retrieved 11th February, 2019].

Asiago, V. M., Alvarado, L. Z., Shanaiah, N., Gowda, G. A. N., Owusu-sarfo, K., Ballas, R. and Raftery, D. (2011). Early detection of recurrent breast cancer using metabolite profiling. *Cancer Res*. 70: 8309-8318.

Atanasov, A. G., Waltenberger, B., Pferschy-Wenzig, E. M., Linder, T., Wawrosch, C., Uhrin, P., Temml, V., Wang, L., Schwaiger, S., Heiss, E. A., Rollinger, J. M., Schuster, D., Breuss, J. M., Bochkov, V., Mihovilovic, M. D., Kopp, B., Bauer, R., Dirsch, V. M. and Stuppner, H. (2015). Discovery and resupply of pharmacologically active plant-derived natural products : a review. *Biotechnol. Adv*. 33: 1582-1614.

Atjanasuppat, K., Wongkham, W., Meepowpan, P., Kittakoop, P., Sobhon, P., Bartlett, A. and Whitfield, P. J. (2009). In vitro screening for anthelmintic and antitumour activity of ethnomedicinal plants from Thailand. *J. Ethnopharmacol*. 123: 475-482.

Azim, H. A., Azambuja, E. D, Colozza, M., Bines, J. and Piccart, M. J. (2011). Long-term toxic effects of adjuvant chemotherapy in breast cancer. *Ann. Oncol*. 22: 1939-1947.

Azizah, A. M., Hashimah, B., Nirmal, K., Siti Zubaidah, A. R., Puteri, N. A., Nabihah, A., Sukumaran, R., Balqis, B., Nadia, S. M. R., Sharifah, S. S. S., Rahayu, O., Nur Alham, O. and Azlina, A. A. (2019). Malaysia national cancer registry report 2012-2016. *Ministry of Health, Malaysia*.

Badisa, R. B., Ayuk-Takem, L. T., Ikediobi, C. O. and Walker, E. H. (2006). Selective anti-cancer activity of pure Licamichauxiioic-B acid in cultured cell lines. *Pharm. Biol*. 44: 141-145.

Badisa, R. B., Darling-Reed, S. F., Joseph, P., Cooperwood, J. S., Latinwo, L. M. and Goodman, C. B. (2010). Selective cytotoxic activities of two novel synthetic drugs on human breast carcinoma MCF-7 cells. *Anti-cancer Res*. 29: 2993-2996.

Baharum, Z., Taufiq-yap, Y. H., Hamid, R. A., Kasran, R., Sciences, H., Board, M. C. and Road, N. (2014). In Vitro antioxidant and antiproliferative activities of methanolic plant part extracts of *Theobroma cacao*. *Molecules* 19: 18317-18331.

Begicevic, R. R. and Falasca, M. (2017). ABC Transporters in cancer stem cells: Beyond chemoresistance. *Int. J. Mol. Sci.* 18: 2362.

Belkahla, S., Khan, A. U. H., Gitenay, D., Alexia, C., Gondeau, C., Vo, D-. N., Orecchioni, S., Talarico, G., Bertolini, F., Cartron, G., Hernandez, J., Daujat-Chavanieu, M., Allende-Vega, N. and Gonzalez, M. V. (2018). Changes in metabolism affect expression of ABC transporters through ERK5 and depending on p53 status. *Oncotarget* 9: 1114-1129.

Berdy, J. (2005). Bioactive microbial metabolites. *J. Antibiot.* 58: 1-26.

Bochner, B. R., Siri, M., Huang, R. H., Noble, S., Lei, X., Clemons, P. A. and Wagner, B. K. (2011). Assay of the multiple energy-producing pathways of mammalian cells. *PLoS ONE* 6: e18147.

Bodeker, G. (2012). Integrative oncology meets immunotherapy: new prospects for combination therapy grounded in eastern medical knowledge. *Chin. J. Integr. Med*. 18: 652-662.

Borthwick, A. D. (2012). 2,5-diketopiperazines: synthesis, reactions, medicinal chemistry and bioactive natural products. *Chem. Rev*. 112: 3641-3716.

Boyd, M. R. (1997). The NCI in vitro anti-cancer drug discovery screen. In *Anti-cancer Drug Development Guide*, ed. B. A. Teicher, pp. 23-42. Totowa: Humana Press.

Branco, A. F., Sampaio, S. F., Moreira, A. C., Holy, J., Wallace, K. B., Baldeiras, I., Oliveira, P. J., Sardão, V. A. (2012). Differentiation-dependent doxorubicin toxicity on H9c2 cardiomyoblasts. *Cardiovasc. Toxicol.* 12: 326-340.

Bras, M., Queenan, B. and Susin, S. A. (2005). Programmed cell death via mitochondria: different modes of dying. *Biochem. (Mosc)* 70: 231-239.

Bratchkova, A. and Ivanova, V. (2011). Bioactive metabolites produced by microorganisms collected in Antarctica and the Arctic. *Biotechnol. Biotechnol. Equip*. 25: 1-7.

Brauns, S. C., Milne, P., Naude, R. and Venter, M. V. D. (2004). Selected cyclic dipeptides inhibit cancer cell growth and induce apoptosis in HT-29 colon cancer cells. *Anti-cancer Res*. 24: 1713-1720.

Bredholt, H., Fjærvik, E., Johnsen, G. and Zotchev, S. B. (2008). Actinomycetes from sediments in the Trondheim fjord, Norway: diversity and biological activity. *Mar. Drugs* 6: 12-24.

Broker, L. E., Kruyt, F. A. E. and Giaccone, G. (2005). Cell death independent of caspases: a review. *Clin. Cancer Res*. 11: 3155-3163.

Bruntner, C., Binder, T., Pathom-Aree, W., Goodfellow, M., Bull, A. T., Potterat, O., Puder, C., Horer, S., Schmid, A., Bolek, W., Wagner, K., Mihm, G. and Fiedler,

H. P. (2005). Frigocyclinone, a novel angucyclinone antibiotic produced by a *Streptomyces griseus* strain from Antarctica. *J. Antibiot.* 58: 346-349.

Busi, S. and Pattnaik, S. S. (2018). Current status and applications of actinobacteria in the production of anti-cancerous compounds. In *Actinobacteria: Diversity and Biotechnological Applications*, ed. B. Singh, V. Gupta, and A. Passari, pp. 137-153. The Netherlands: Elsevier Press.

Caesar, L. K. and Cech, N. B. (2019). Synergy and antagonism in natural product extracts: when 1 + 1 does not equal 2. *Nat. Prod. Rep*. 36: 869-888.

Cai, L., Qin, X., Xu, Z., Song, Y., Jiang, H., Wu, Y., Ruan, H. and Chen, J. (2019). Comparison of cytotoxicity evaluation of anti-cancer drugs between real-time cell analysis and CCK−8 method. *ACS Omega* 4: 12036-12042.

Callahan, R. and Hurvitz, S. (2011). HER2-positive breast cancer: current management of early, advanced, and recurrent disease. *Curr. Opin. Obstet. Gynecol.* 23: 37-43.

Carlson, E. E. (2011). Natural products as chemical probes. *ACS Chem. Biol.* 5: 639-653.

Carnero, A. (2002). Targeting the cell cycle for cancer therapy. *Br. J. Cancer* 87: 129-133.

Cheah, Y. K., Lee, L. H., Yun, C., Chieng, C. C-Y. and Wong, C. M. V-L. (2015). Isolation, identification and screening of Actinobacteria in volcanic soil of Deception Island (the Antarctic) for antimicrobial metabolites. *Pol. Polar Res.* 36: 67-78.

Chen, C., Ye, Y., Wang, R., Zhang, Y., Wu, C., Debnath, S. C., Ma, Z., Wang, J. and Wu, M. (2018). *Streptomyces nigra* sp. nov. is a novel actinobacterium isolated from mangrove soil and exerts a potent antitumour activity *in vitro*. *Front. Microbiol*. 9: 1587.

Chen, D., Yu, J. and Zhang, L. (2016). Necroptosis: an alternative cell death program defending against cancer. *Biochim. Biophys. Acta* 1865: 228-236.

Chen, Y., Mahieu, N. G., Huang, X., Singh, M., Crawford, P. A., Johnson, S. L., Gross, R. W., Schaefer, J. and Patti, G. J. (2017). Lactate metabolism is associated with mammalian mitochondria. *Nat. Chem. Biol*. 12: 937-943.

Cheng, S., Seo, J., Huang, B. T., Napolitano, T. and Champeil, E. (2016). Mitomycin C and decarbamoyl mitomycin C induce p53-independent $p21^{WAF1/CIP1}$ activation. *Int. J. Oncol*. 49: 1815-1824.

Cheong, H., Lu, C., Lindsten, T. and Thompson, C. B. (2012). Therapeutic targets in cancer cell metabolism and autophagy. *Nat. Biotechnol.* 30: 671-678.

Choi, Y. H. and Yoo, Y. H. (2012). Taxol-induced growth arrest and apoptosis is

associated with the upregulation of the Cdk inhibitor, $p21^{WAF1/CIP1}$, in human breast cancer cells. *Oncol. Rep*. 28: 2163-2169.

Cluntun, A. A., Lukey, M. J., Cerione, R. A. and Locasale, J. W. (2018). Glutamine metabolism in cancer: understanding the heterogeneity. *Trends Cancer* 3: 169-180.

Cuyàs, E., Corominas-faja, B. and Menendez, J. A. (2014). The nutritional phenome of EMT-induced cancer stem-like cells. *Oncotarget* 5: 3970-3982.

Dang, C.V. (2012). Links between metabolism and cancer. *Genes Dev.* 26: 877-890.

Das, G. C., Holiday, D., Gallardo, R. and Haas, C. (2001). Taxol-induced cell cycle arrest and apoptosis: dose-response relationship in lung cancer cells of different wild-type p53 status and under isogenic condition. *Cancer Lett.* 165: 147-153.

Demain, A. L. and Sanchez, S. (2009). Microbial drug discovery: 80 years of progress. *J. Antibiot.* 62: 5-16.

Dhaneesha, M., Naman, C. B., Krishnan, K. P., Sinha, R. K., Jayesh, P., Joseph, V., Bright-Singh, I. S., Gerwick, W. H. and Sajeevan, T. P. (2017). *Streptomyces artemisiae* MCCB 248 isolated from Arctic fjord sediments has unique PKS and NRPS biosynthetic genes and produces potential new anti-cancer natural products. *3 Biotech* 7: 32.

Diaz-Cardenas, C., Cantillo, A., Rojas, L. Y., Sandoval, T., Fiorentino, S., Robles, J., Ramos, F. A., Zambrano, M. M. and Baena, S. (2017). Microbial diversity of saline environments: searching for cytotoxic activities. *AMB Expr*. 7: 223.

Dowlati, A., Posey, J., Ramanathan, R. K., Rath, L., Fu, P., Chak, A., Krishnamurthi, S., Brell, J., Ingalls, S., Hoppel, C. L., Ivy, P. and Remick, S. C. (2009). Phase II and pharmacokinetic trial of rebeccamycin analog in advanced biliary cancers. *Cancer Chemother. Pharmacol.* 65: 73-78.

Eisenbrand, G., Pool-zobel, B., Baker, V., Balls, M., Blaauboer, B. J., Boobis, A., Carereg, A., Kevekordesh, S., Lhuguenoti, J.-C., Pieterse, R. and Kleiner, J. (2002). Methods of in vitro toxicology. *Food Chem. Toxicol*. 40: 193-236.

Eleazu, C. O., Eleazu, K. C., Chukwuma, S. and Essien, U. N. (2013). Review of the mechanism of cell death resulting from streptozotocin challenge in experimental animals, its practical use and potential risk to humans. *J. Diabetes Metab. Disord.* 12: 60.

Encheva-Malinova, M., Stoyanova, M., Avramova, H., Pavlova, Y., Gocheva, B., Ivanova, I. and Moncheva, P. (2014). Antibacterial potential of *Streptomycete* strains from Antarctic soils. *Biotechnol. Biotechnol. Equip.* 28: 721-727.

Eroles, P., Bosch, A., Pérez-fidalgo, J. A. and Lluch, A. (2012). Molecular biology in breast cancer: intrinsic subtypes and signaling pathways. *Cancer Treat. Rev.* 38: 698-707.

Fadaka, A., Ajiboye, B., Ojo, O., Adewale, O., Olayide, I. and Emuowhochere, R. (2017). Biology of glucose metabolization in cancer cells. *J. Oncol. Sci.* 3: 45-51.

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. *Int. J. Cancer* 136: 359-386.

Finn, R. S., Aleshin, A. and Slamon, D. J. (2016). Targeting the cyclin-dependent kinases (CDK) 4/6 in estrogen receptor-positive breast cancers. *Breast Cancer Res.* 18: 1-11.

Franco-Correa, M., Quintana, A., Duque, C., Suarez, C., Rodr ́guez, M. X. and Barea, J. M. (2010). Evaluation of actinomycete strains for key traits related with plant growth promotion and mycorrhiza helping activities. *Appl. Soil Ecol.* 45: 209-217.

Fulda, S. (2013). The mechanism of necroptosis in normal and cancer cells. *Canc. Biol. Ther.* 14: 999-1004.

Fulda, S. and Vucic, D. (2012). Targeting IAP proteins for therapeutic intervention in cancer. *Nat. Rev. Drug Discov.* 11: 109-124.

Galm, U., Hager, M. H., Van Lanen, S. G., Ju, J., Thorson, J. S. and Shen, B. (2005). Antitumour antibiotics: bleomycin, enediynes, and mitomycin. *Chem. Rev.* 105: 739-58.

Gao, G., Chen, L. and Huang, C. (2014). Anti-cancer drug discovery: update and comparisons in yeast, drosophila, and zebrafish. *Curr. Mol. Pharmacol.* 7: 44-51.

Gao, X., Lu, Y., Xing, Y., Ma, Y., Lu, J., Bao, W., Wang, Y. and Xi, T. (2012). A novel anti-cancer and antifungus phenazine derivative from a marine actinomycete BM-17. *Microbiol. Res.* 167: 616-622.

Gesheva, V. and Vasileva-Tonkova, E. (2012). Production of enzymes and anti-microbial compounds by halophilic Antarctic *Nocardioides sp.* grown on different carbon sources. *World J. Microbiol. Biotechnol.* 28: 2069-2076.

Giddings, L. A. and Newman, D. J. (2013). Microbial natural products: molecular blueprints for antitumour drugs. *J. Ind. Microbio.l Biotechnol.* 40: 1181-1210.

Gillet, J. and Gottesman, M. M. (2010). Multi-drug resistance in cancer. *Methods Mol. Biol.* 596: 47-76.

Goekkurt, E., Al-Batran, S. E., Mogck, U., Pauligk, C., Hartmann, J. T., Kramer, M., Jaeger, E., Ehninger, G. and Stoehlmacher, J. (2009). Pharmacogenetic analyses of hematotoxicity in advanced gastric cancer patients receiving biweekly fluorouracil, leucovorin, oxaliplatin and docetaxel (FLOT): a

translational study of the Arbeitsgemeinschaft Internistische Onkologie (AIO). *Ann. Oncol.* 20: 481-485.

Gokulan, K., Khare, S. and Cerniglia, C. (2014). Metabolic pathways: production of secondary metabolites of bacteria. In *Encyclopedia of Food Microbiology*, ed. C. A. Batt, and M. L. Tortorello, pp. 561-569. The Netherlands: Elsevier Press.

Gotwals, P., Cameron, S., Cipolletta, D., Cremasco, V., Crystal, A., Hewes, B., Mueller, B., Quaratino, S., Sabastos-Peyton, C., Petruzzelli, L., Engelman, J. A. and Dranoff, G. (2017). Prospects for combining targeted and conventional cancer therapy with immunotherapy. *Nat. Rev. Cancer* 17: 286-301.

Green, D. R. and Evan, G. I. (2002). A matter of life and death. *Cancer Cell* 1: 19-30.

Han, S. R., Kim, K. H., Ahn, D. H., Park, H. and Oh, T. J. (2016). Complete genome sequence of carotenoid-producing *Microbacterium sp*. strain PAMC28756 isolated from an Antarctic lichen. *J. Biotechnol.* 226: 18-19.

Hanahan, D. and Weinberg, R. A. (2011). Review hallmarks of cancer: the next generation. *Cell* 144: 646-674.

Harwood, S. M., Yaqoob, M. M. and Allen, D. A. (2005). Review article caspase and calpain function in cell death: bridging the gap between apoptosis and necrosis. *Ann. Clin. Biochem*. 42: 415-431.

Hassan, M., Watari, H., Abualmaaty, A., Ohba, Y. and Sakuragi, N. (2014). Apoptosis and molecular targeting therapy in cancer. *Biomed. Res. Int.* 2014: 150845.

Hejmadi, M. (2013). *Introduction to Cancer Biology*. pp. 1-48. Denmark: Ventus Publishing.

Ho, L. K. and Nodwell, J. R. (2016). David and Goliath: chemical perturbation of eukaryotes by bacteria. *J. Ind. Microbiol. Biotechnol.* 43: 233-248.

Huang, R., Zhou, X., Xu, T., Yang, X. and Liu, Y. (2010). Diketopiperazines from marine organisms. *Chem. Biodivers*. 7: 2809-2829.

Ito, A., Shintaku, I., Satoh, M., Ioritani, N., Aizawa, M., Tochigi, T., Kawamura, S., Aoki, H., Numata, I., Takeda, A., Namiki, S., Namima, T., Ikeda, Y., Kambe, K., Kyan, A., Ueno, S., Orikasa, K., Katoh, S., Adachi, H., Tokuyama, S., Ishidoya, S., Yamaguchi, T. and Arai, Y. (2013). Prospective randomized phase II trial of a single early intravesical instillation of pirarubicin (THP) in the prevention of bladder recurrence after nephroureterectomy for upper urinary tract urothelial carcinoma: the THP monotherapy study group trial. *J. Clin. Oncol.* 31: 1422-1427.

Ivanova, V., Kolarova, M., Aleksieva, K., Grafe, U., Dahse, H. M. and Laatsch, H. (2007). Microbiaeratin, a new natural indole alkaloid from a *Microbispora aerata*, isolated from Livingston Island, Antarctica. *Prep. Biochem. Biotechnol.* 37: 161-168.

Ivanova, V., Laatsch, H., Kolarova, M. and Aleksieva, K. (2013). Structure elucidation of a new natural diketopiperazine from a *Microbispora aerata* strain isolated from Livingston Island, Antarctica. *Nat. Prod. Res.* 27: 164-170.

Jain, M., Nilsson, R., Sharma, S., Madhusudhan, N., Kitami, T., Souza, A. L., Kafri, R., Kirschner, M. W., Clish, C. B. and Mootha, V. K. (2012). Metabolite profiling identifies a key role for glycine in rapid cancer cell proliferation. *Science* 336: 1040-1044.

Jatoi, I., Anderson, W. F., Jeong, J. H. and Redmond, C. K. (2011). Breast cancer adjuvant therapy: time to consider its time-dependent effects. *J. Clin. Oncol.* 29: 2301-2304.

Jiang, S.-H., Dong, F.-Y., Da, L.-T., Yang, X.-M., Wang, X.-X., Weng, J.-Y., Feng, L., Zhu, L.-L., Zhang, Y.-L., Zhang, Z.-G., Sun, Y.-W., Li, J. and Xu, M.-J. (2020). Ikarugamycin inhibits pancreatic cancer cell glycolysis by targeting hexokinase 2. *FASEB J*. 34: 3943-3955.

Jiang, Y., Pan, Y., Rhea, P. R., Tan, L., Gagea, M., Cohen, L., Fischer, S. M. and Yang, P. (2017). A sucrose-enriched diet promotes tumorigenesis in mammary gland in part through the 12-lipoxygenase pathway. *Cancer Res*. 76: 24-29.

Kanaan, Y. M., Sampey, B. P., Beyene, D., Esnakula, A. K., Naab, T. J., Ricks-santi, L. J., Dasi, S., Day, A., Blackman, K. W., Frederick, W., Copeland, R. L., Gabrielson, E. and Dewitty, R. L. (2014). Metabolic profile of triple-negative breast cancer in African–American women reveals potential biomarkers of aggressive disease. *Cancer Genom. Proteom*. 11: 279-294.

Karanam, G., Arumugam, M. K. and Natesh, N. S. (2019). Anti-cancer effect of marine sponge-associated *Bacillus pumilus* AMK1 derived dipeptide cyclo (-Pro-Tyr) in human liver cancer cell line through apoptosis and G2/M phase arrest. *Int. J. Pept. Res. Ther*. 26: 445-457.

Karna, P. and Yang, L. (2009). Apoptotic signaling pathway and resistance to apoptosis in breast cancer stem cells. In *Apoptosis in Carcinogenesis and Chemotherapy*, ed. G.G. Chen, and P. B. Lai, pp. 1-23. Dordrecht: Springer.

Kaufmann, S. H. and Vaux, D. L. (2003). Alterations in the apoptotic machinery and their potential role in anti-cancer drug resistance. *Oncogene* 22: 7414-7430.

Ke, N., Wang, X., Xu, X. and Abassi, A. (2011). The xCELLigence system for real-time and label-free monitoring of cell viability. *Methods Mol. Biol.* 740: 33-43.

Kim, E. J., Kim, G. T., Kim, B. M., Lim, E. G., Kim, S. Y. and Kim, Y. M. (2017). Apoptosis-induced effects of extract from Artemisia annua Linné by modulating PTEN/p53/PDK1/Akt/ signal pathways through PTEN/p53-independent manner in HCT116 colon cancer cells. *BMC Complement. Altern. Med*. 17: 236.

Kim, H., Lee, K., Kim, S., Kwon, Y. and Choi, H. (2016). Comparative metabolic and

lipidomic profiling of human breast cancer cells with different metastatic potentials. *Oncotarget* 7: 67111-67128.

Kim, K. W., Roh, J. K., Wee, H. J. and Kim, C. (2016). Natural product anti-cancer drugs. In *Cancer Drug Discovery: Science and History*, pp. 113-134. Dordrecht: Springer.

Kondo, Y., Kanzawa, T., Sawaya, R. and Kondo, S. (2005). The role of autophagy in cancer development and response to therapy. *Nat. Rev. Cancer* 5: 726-734.

Kong, R. (2005). LC/MS application in high-throughput ADME screen. In *Handbook of Pharmaceutical Analysis by HPLC*, ed. S. Ahuja, and M. W. Dong, pp. 413-446. The Netherlands: Elsevier Press.

Krause, J. and Tobin, G. (2013). Discovery, development, and regulation of natural products. In *Using Old Solutions to New Problems-Natural Drug Discovery in the 21st Century*, ed. M. Kulka, pp. 1-35. London: InTechOpen.

Kulakova, L., Galkin, A., Nakayama, T., Nishino, T. and Esaki, N. (2004). Cold-active esterase from *Psychrobacter* sp. Ant300: gene cloning, characterization, and the effects of Gly→Pro substitution near the active site on its catalytic activity and stability. *Biochim. Biophys. Acta* 1696: 59-65.

Kumar, B., Singh, S., Skvortsova, I. and Kumar, V. (2017). Promising targets in anti-cancer drug development: recent updates. *Curr. Med. Chem.* 24: 4729-4752.

Kumar, S. N., Mohandas, C., Siji, J. V., Rajasekharan, K. N. and Nambisan, B. (2012). Identification of antimicrobial compound, diketopiperazines, from a *Bacillus* sp. N strain associated with a rhabditid entomopathogenic nematode against major plant pathogenic fungi. *J. Appl. Microbiol*. 113: 914-924.

Kumar, S. N., Siji, J. V., Nambisan, B. and Mohandas, C. (2012). Activity and synergistic antimicrobial activity between diketopiperazines against bacteria *in vitro*. *Appl. Biochem. Biotechnol*. 168: 2285-2296.

Kurapova, I., Zenova G. M., Sudnitsyn I. I., Kizilova A. K., Manucharova N. A., Norovsuren Z. H. and Zvyagintsev, D. G. (2012). Thermotolerant and thermophilic actinomycetes from soils of Mongolia Desert Steppe Zone. *Microbiol.* 81: 98-108.

Kurtboke, D. I. (2012). Biodiscovery from rare actinomycetes: an eco-taxonomical perspective. *Appl. Microbiol. Biotechnol*. 93: 1843-1852.

Kvolik, S., Jukic, M., Matijevic, M. and Marjanovic, K. (2010). An overview of coagulation disorders in cancer patients. *Surg. Oncol.* 19: 33-46.

Law, B. K. (2005). Rapamycin: an anti-cancer immunosuppressant. *Crit. Rev. Oncol. Hematol.* 56: 47-60.

Lee, L. H, Cheah, Y. K., Sidik, S. M., Mutalib, N.-S. A., Tang, Y.-L., Lin, H.-P. and

Hong, K. (2012). Molecular characterization of Antarctic actinobacteria and screening for antimicrobial metabolite production. *World J. Microbiol. Biotechnol.* 28: 2125-2137.

Lee, L. H., Cheah, Y. K., Sidik, S. M., Xie, Q. Y., Tang, Y. -L., Lin, H. -P., Mutalib, N. S. A. and Hong, K. (2013). Actinobacterium of the family *Dermacoccaceae*. *Int. J. Syst. Evol. Microbiol.* 63: 1-10.

Lee, S. D. (2013). *Tamlicoccus marinus* gen. nov., sp. nov., isolated from seawater. *Int. J. Syst. Evol. Microbiol*. 63: 1951-1954.

Lee, S. L. (2015). *Anti-cancer and antibacterial properties of bioactive fractions of Barrientosiimonas humi, novel actinobacteria from Antarctica*. (Unpublished final year project). Universiti Putra Malaysia.

Levine, B. (2007). Cell biology: autophagy and cancer. *Nature* 446: 745-747.

Li, C., Zhang, G., Zhao, L., Ma, Z. and Chen, H. (2016). Metabolic reprogramming in cancer cells: glycolysis, glutaminolysis, and Bcl-2 proteins as novel therapeutic targets for cancer. *World J. Surg. Oncol*. 14: 15.

Li, J., Kim, S. G. and Blenis, J. (2014). Rapamycin: one drug, many effects. *Cell Metab.* 19: 373-379.

Li, Y., Li, R., Liu, Q., Li, W., Zhang, T., Zou, M., Li, H., Wu, T., Cheng, S., Su, Z., Zhang, Z. and He, J. (2016). One-step self-assembling nanomicelles for pirarubicin delivery to overcome multidrug resistance in breast cancer. *Mol. Pharm.* 13: 3934-3944.

Li, Y., Zhuang, H., Zhang, X., Li, Y., Liu, Y., Yi, X., Qin, G., Wei, W. and Chen, R. (2018). Multiomics integration reveals the landscape of prometastasis metabolism in hepatocellular carcinoma. *Mol. Cell. Proteomics* 17: 607-618.

Liang, X., Zhang, L., Natarajan, S. K. and Becker, D. F. (2013). Proline mechanisms of stress survival. *Antioxid. Redox Signal*. 19: 998-1011.

Lichota, A. and Gwozdzinski, K. (2018). Anti-cancer activity of natural compounds from
plant and marine environment. *Int. J. Mol. Sci.* 19: 3533.

Lieberman, J. and Fan, Z. (2003). Nuclear war: the granzyme A-bomb. *Curr. Opin. Immunol*. 15: 553-559.

Lin, Z. and Will, Y. (2012). Evaluation of drugs with specific organ toxicities in organ-specific cell lines. *Toxicol. Sci*. 126: 114-127.

Lindley, C. and Michaud, L. B. (2005). Breast Cancer. In *Pharmacotherapy: A Pathophysiologic Approach*, ed. J. T. Dipiro, pp. 2329-2361. New York: McGraw-Hill.

Linnert, M. and Gehl, J. (2009). Bleomycin treatment of brain tumours: an evaluation.

Anti-cancer Drugs 20: 157-164.

Lippert, T. H., Ruoff, H.-J. and Volm, M. (2008). Intrinsic and acquired drug resistance in malignant tumours. *Drug Res.* 58: 261-264.

Lockshin, R. A. and Zakeri, Z. (2001). Programmed cell death and apoptosis: origins of the theory. *Nat. Rev. Mol. Cell Biol.* 2: 545-550.

Lockshin, R. A. and Zakeri, Z. (2004). Apoptosis, autophagy, and more. *Int. J. Biochem. Cell Biol.* 36: 2405-2419.

Lombo, F., Menendez, N., Salas, J. A. and Mendez, C. (2006). The aureolic acid family of antitumour compounds: structure, mode of action, biosynthesis, and novel derivatives. *Appl. Microbiol. Biotechnol.* 73: 1-14.

Looi, C. Y., Arya, A., Cheah, F. K., Muharram, B., Leong, K. H., Mohamad, K., Wong, W. F., Rai, N. and Mustafa, M. R. (2013). Induction of apoptosis in human breast cancer cells via caspase pathway by vernodalin isolated from *Centratherum anthelminticum* (L.) seeds. *PLoS One* 8: e56643.

Lowe, S. W. and Lin, A. W. (2000). Apoptosis in cancer. *Carcinogenesis* 21: 485-495.

Ludwig, W., Euzeby, J., Schumann, P., Busse, H. J., Trujillo, M. E., Kampfer, P. and Whitman, W. B. (2012). Road map of the actinobacteria. In *Bergey's Manual of Systematic Bacteriology*, ed. W. Whitman, M. Goodfellow, P. Kampfer, H. J. Busse, M. Trujillo, W. Ludwig, K. I. Suzuki, and A. Parte, pp. 1-28. New York: Springer.

Macherla, V. R., Liu, J., Bellows, C., Teisan, S., Nicholson, B., Lam, K. S. and Potts, B. C. M. (2005). Glaciapyrroles A, B, and C, pyrrolosesquiterpenes from a *Streptomyces* sp. isolated from an Alaskan marine sediment. *J. Nat. Prod*. 68: 780-783.

Macleod, K. G. and Langdon, S. P. (2004). Essential techniques of cancer cell culture. In *Cancer Cell Culture-Methods and Protocols*, ed. S. P. Langdon, pp. 17-29. New York: Humana Press.

Malumbres, M. and Barbacid, M. (2007). Cell cycle kinases in cancer. *Curr. Opin. Genet. & Dev*. 17: 60-65.

Mandic, A., Viktorsson, K., Strandberg, L., Heiden, T., Hansson, J., Linder, S. and Shoshan, M. C. (2002). Calpain-mediated Bid cleavage and calpain-independent Bak modulation: two separate pathways in cisplatin-induced apoptosis. *Mol. Cell Biol*. 22: 3003-3013.

Manivasagan, P., Venkatesan, J., Sivakumar, K. and Kim, S. K. (2014). Pharmaceutically active secondary metabolites of marine. *Microb. Res.* 169: 262-278.

Margolis, J. and Grever, M. R. (2000). Pentostatin (Nipent): a review of potential toxicity and its management. *Semin. Oncol.* 27: 9-14.

Marlina, S., Shu, M. H., AbuBakar, S. and Zandi, K. (2015). Development of a Real-Time Cell Analysing (RTCA) method as a fast and accurate screen for the selection of chikungunya virus replication inhibitors. *Parasit. Vectors* 8: 579.

Mathiasen, I. S., Sergeev, I. N., Bastholm, L., Elling, F., Norman, A. W. and Jaattela, M. (2002). Calcium and calpain as key mediators of apoptosis-like death induced by vitamin D compounds in breast cancer cells. *J. Biol. Chem*. 277: 30738-30745.

Mccleland, K., Milne, P. J., Lucieto, F. R., Frost, C., Brauns, S. C., Van De Venter, M., Du Plessis, J. and Dyason, K. (2004). An investigation into the biological activity of the selected histidine-containing diketopiperazines cyclo (His-Phe) and cyclo (His-Tyr). *J. Pharm. Pharmacol*. 56: 1143-1153.

Miller, R. B. and Case, W. S. (2011). Radial chromatography for the separation of nitroaniline isomers. *J. Chem. Educ*. 88: 1328-1330.

Millimouno, F. M., Dong, J., Yang, L., Li, J. and Li, X. (2014). Targeting apoptosis pathways in cancer and perspectives with natural compounds from Mother Nature. *Cancer Prev. Res.* 7: 1081-1108.

Mishra, P. and Ambs, S. (2015). Metabolic signatures of human breast cancer. *Mol. Cell. Oncol*. 2: e992217.

Mladenka, P., Applova, L., Patocka, J., Costa, V. M., Remiao, F., Pourova, J., Mladenka, A., KarlIckova, J., Jahodar, L., VoprSalova, M., Varner, K. J. and Sterba, M. (2018). Comprehensive review of cardiovascular toxicity of drugs and related agents. *Med. Res. Rev.* 38: 1332-1403.

Moon, K., Ahn, C.-H., Shin, Y., Won, T. H., Ko, K., Lee, S. K., Oh, K.-B., Shin, J., Nam, S, I. and Oh, D.-C. (2014). New benzoxazine secondary metabolites from an arctic actinomycete. *Mar. Drugs* 12: 2526-2538.

Mosmann, T. (1983). Rapid colorimetric assay for cellular growth and survival: application to proliferation and cytotoxicity assays. *J. Immunol. Methods* 65: 55-63.

Mushtaq, S., Abbasi, B. H., Uzair, B. and Abbasi, R. (2018). Natural products as reservoirs of novel therapeutic agents. *EXCLI J.* 17: 420-451.

Nakano, A., Abe, M., Tsuji, D., Miki, H., Ikegame, A., Nakamura, S., Harada, T., Fujii, S., Kagawa, K., Takeuchi, K., Ozaki, S., Itoh, K. and Matsumoto, T. (2011). Inhibition of hexokinase II inactivates ABC transporters and restores drug sensitivity in myeloma cells. *Blood* 118: 135.

Narvaez, C. J. and Welsh, J. (2001). Role of mitochondria and caspases in vitamin D-mediated apoptosis of MCF-7 breast cancer cells. *J. Biol. Chem*. 276: 9101-9107.

Newman, D. J. and Cragg, G. M. (2016). Natural products as sources of new drugs

from 1981 to 2014. *J. Nat. Prod.* 79: 629-661.

Newman, D. J. and Cragg, G. M. (2012). Natural products as sources of new drugs over the 30 years from 1981 to 2010. *J. Nat. Prod.* 75: 311-335.

Newman, D. J. and Hill, R. T. (2006). New drugs from marine microbes: the tide is turning. *J. Ind. Microbiol. Biotechnol.* 33: 539-544.

Nicholson, B., Lloyd, G. K., Miller, B. R., Michael, A., Kiso, Y., Hayashi, Y. and Neuteboom, S. T. (2006). NPI-2358 is a tubulin-depolymerizing agent: in-vitro evidence for activity as a tumour vascular-disrupting agent. *Anti-Cancer Drugs* 17: 25-31.

Nikoletopoulou, V., Markaki, M., Palikaras, K. and Tavernarakis, N. (2013). Crosstalk between apoptosis, necrosis and autophagy. *Biochim. Biophys. Acta* 1833: 3448-3459.

Nock, C. J., Brell, J. M., Bokar, J. A., Cooney, M. M., Cooper, B., Gibbons, J., Krishnamurthi, S., Manda, S., Savvides, P., Remick, S. C., Ivy, P. and Dowlati, A. (2011). A phase I study of rebeccamycin analog in combination with oxaliplatin in patients with refractory solid tumours. *Invest. New Drugs* 29: 126-130.

Norberg, E., Gogvadze, V., Ott, M., Horn, M., Uhlen, P., Orrenius, S. and Zhivotovsky, B. (2008). An increase in intracellular Ca2+ is required for the activation of mitochondrial calpain to release AIF during cell death. *Cell Death Differ.* 15: 1857-1864.

Nordin, M. L., Kadir, A. A., Zakaria, Z. A., Abdullah, R. and Abdullah, M. N. H. (2018). *In vitro* investigation of cytotoxic and antioxidative activities of *Ardisia crispa* against breast cancer cell lines, MCF-7 and MDA-MB-231. *BMC Complement. Altern. Med.* 18: 87.

Núñez-Montero, K. and Barrientos, L. (2018). Advances in Antarctic research for antimicrobial discovery: a comprehensive narrative review of bacteria from Antarctic environments as potential sources of novel antibiotic compounds against human pathogens and microorganisms of industrial importance. *J. Antibiot.* 7: 90.

Ofengeim, D. and Yuan, J. (2013). Regulation of RIP1 kinase signalling at the crossroads of inflammation and cell death. *Nat. Rev. Mol. Cell Biol.* 14: 727-736.

Olsson, M. and Zhivotovsky, B. (2011). Caspases and cancer. *Cell Death Differ.* 18: 1441-1449.

Oncul, S. and Ercan, A. (2017). Discrimination of the effects of doxorubicin on two different breast cancer cell lines on account of multidrug resistance and apoptosis. *Indian J. Pharm. Sci.* 79: 599-607.

Onrust, S. V. and Lamb, H. M. (1999). Valrubicin. *Drugs Aging* 15: 69-75.

Orrenius, S., Nicotera, P. and Zhivotovsky, B. (2011). Cell death mechanisms and their implications in toxicology. *Toxicol. Sci*. 119: 3-19.

Pai, V. and Nahata, M. (2000). Cardiotoxicity of chemotherapeutic agents: incidence, treatment and prevention. *Drug Saf.* 22: 263-302.

Papaioannou, N. E., Beniata, O. V., Vitsos, P., Tsitsilonis, O. and Samara, P. (2016). Harnessing the immune system to improve cancer therapy. *Ann. Transl. Med*. 4: 261-276.

Parag, B., Sasikala, C. and Ramana, C. V. (2015). *Barrientosiimonas endolithica* sp. nov., isolated from pebbles, reclassification of the only species of the genus *Tamlicoccus*, *Tamlicoccus marinus* Lee 2013, as *Barrientosiimonas marina comb*. nov. and emended description of the genus *Barrientosiimonas. Int. J. Syst. Evol. Microbiol*. 65: 3031-3036.

Pasparakis, M. and Vandenabeele, P. (2015). Necroptosis and its role in inflammation. *Nature* 517: 311-320.

Pei, J., Liu, C., Hsu, Y., Lin, L., Wang, S., Chung, J., Bau, D. and Lin, S. (2012). Amentoflavone induces cell-cycle arrest and apoptosis in MCF-7 human breast cancer cells via mitochondria-dependent pathway. *In Vivo* 26: 963-970.

Pettit, R. K. (2004). Soil DNA libraries for anti-cancer drug discovery. *Cancer Chemother. Pharmacol*. 54: 1-6.

Picot, M. C. N., Bender, O., Atalay, A., Zengin, G., Loffredo, L., Hadji-Minaglou, F. and Mahomoodally, M. F. (2017). Multiple pharmacological targets, cytotoxicity, and phytochemical profile of Aphloia theiformis (Vahl.) Benn. *Biomed. Pharma*. 89: 342-350.

Public Health England (2013). Cell counting using a haemocytometer. Available: https://www.phe-culturecollections.org.uk/technical/cell-culture-protocols/cellcounting.aspx [Retrieved 20th October 2018].

Qi, S., Kou, X., Lv, J., Qi, Z. and Yan, L. (2015). Ampelopsin induces apoptosis in HepG2 human hepatoma cell line through extrinsic and intrinsic pathways: involvement of P38 and ERK. *Environ. Toxicol. Pharmacol*. 40: 847-854.

Qu, X., Yu, J., Bhagat, G., Furuya, N., Hibshoosh, H., Troxel, A., Rosen, J., Eskelinen, E. L., Mizushima, N., Ohsumi, Y., Cattoretti, G. and Levine, B. (2003). Promotion of tumorigenesis by heterozygous disruption of the beclin 1 autophagy gene. *J. Clin. Invest.* 112: 1809-1820.

Ravikumar, S., Fredimoses, M. and Gnanadesigan, M. (2012). Anti-cancer property of sediment actinomycetes against MCF-7 and MDA-MB-231 cell lines. *Asian Pac. J. Trop. Biomed*. 2: 92-96.

Roemer, T., Xu, D., Singh, S. B., Parish, C. A., Harris, G., Wang, H., Davies, J. E. and Bills, G. F. (2011). Confronting the challenges of natural product-based

antifungal discovery. *Chem. Biol.* 18: 148-164.

Rosandy, A. R., Yeoh, C. Y., Cheah, Y. K., Bakar, M. A., Muhamad, A. and Khalid, R. M. (2019). Psychrotolerant actinobacteria *Barrientosiimonas humi* 39^T as a source of diketopiperazine. *Malaysian J. Anal. Sci*. 23: 748-762.

Ruddy, K. J. and Winer, E. P. (2013). Male breast cancer: risk factors, biology, diagnosis, treatment, and survivorship. *Ann. Oncol.* 24: 1434-1443.

Ruiz, B., Ch ávez, A., Forero, A., Garc á-huante, Y., Romero, A., S ánchez, M., Rocha, D., S ánchez, B., Rodriguez-Sanoja, R., S ánchez, S. and Langley, E. (2010). Production of microbial secondary metabolites: regulation by the carbon source. *Crit. Rev. Microbiol.* 36: 146-167.

Ruiz-Torres, V., Encinar, J. A., Herranz-L ópez, M., P érez-S ánchez, A., Galiano, V., Barraj ón-Catal án, E. and Micol, V. (2017). An updated review on marine anti-cancer compounds: the use of virtual screening for the discovery of small-molecule cancer drugs. *Molecules* 22: 1037.

Saeidnia, S. (2015). Anti-cancer antibiotics. In *New Approaches to Natural Anti-cancer Drugs*, pp. 51-66. Dordrecht: Springer.

Saini, V. K., Sewal, R. K., Ahmad, Y. and Medhi, B. (2015). Prospective observational study of adverse drug reactions of anti-cancer drugs used in cancer treatment in a tertiary care hospital. *Indian J. Pharm. Sci*. 77: 687-693.

Schein, P. S., Macdonald, J. S., Hoth, D. F. and Wooley, P. V. (1979). The FAM (5-fluorouracil, adriamycin, mitomycin C) and SMF (streptozotocin, mitomycin C, 5- fluorouracil) chemotherapy regimens. In *Mitomycin C: Current Status and New Developments*, ed. S. K. Carter, S. T. Crooke, and N. A. Alder, pp. 133-143. The Netherlands: Elsevier Press.

Schmid, I., Krall, W. J., Uittenbogaart, C. H., Braun, J. and Giorgi, J. V. (1992). Dead cell discrimination with 7-amino-actinomycin D in combination with dual color immunofluorescence in single laser flow cytometry. *Cytometry* 13: 204-208.

Schwandt, A., Mekhail, T., Halmos, B., O'brien, T., Ma, P. C., Fu, P., Ivy, P. and Dowlati, A. (2012). Phase-II trial of rebeccamycin analog, a dual topoisomerase-I and -II inhibitor, in relapsed sensitive small cell lung cancer. *J. Thorac. Oncol.* 7: 751-754.

Shajahan-haq, A. N., Cheema, M. S. and Clarke, R. (2015). Application of metabolomics in drug resistant breast cancer research. *Metabolites* 5: 100-118.

Sharma, G. N., Dave, R., Sanadya, J., Sharma, P. and Sharma, K. K. (2010). Various types and management of breast cancer: an overview. *J. Adv. Pharm. Technol. Res.* 1: 109-126.

Shea, A., Wolcott, M., Daefler, S. and Rozak, D. A. (2012). Biolog phenotype microarrays. *Methods Mol. Biol.* 881: 331-373.

Shen, L., O'Shea, J. M., Kaadige, M. R., Cunha, S., Wilde, B. R. and Cohen, A. L. (2015). Metabolic reprogramming in triple-negative breast cancer through Myc suppression of TXNIP. *PNAS* 112: 5425-5430.

Shin, H. J., Mojid Mondol, M. A., Yu, T. K., Lee, H., Lee, Y., Jung, H. J., Kim, H. J. and Kwon, H. J. (2010). An angiogenesis inhibitor isolated from a marine-derived actinomycete, *Nocardiopsis* sp. 03N67. *Phytochem. Lett.* 3: 194-197.

Shivlata, L. and Satyanarayana, T. (2015). Thermophilic and alkaliphilic actinobacteria: biology and potential applications. *Front. Microbiol.* 6: 1-29.

Sibio, A. D., Abriata, G., Buffa, R., Viniegra, M., Forman, D. and Sierra, M. S. (2016). Etiology of breast cancer (C50) in Central and South America. In *Cancer in Central and South America.* Lyon: International Agency for Research on Cancer. Available: http://www-dep.iarc.fr/CSU_resources. html [Retrieved 9th March, 2019].

Siddharth, S. and Sharma, D. (2018). Racial disparity and triple-negative breast cancer in Afican-American women: a multifaceted affair between obesity, biology, and socioeconomic determinants. *Cancers (Basel)* 10: 1-19.

Siddiqui, A. A., Iram, F., Siddiqui, S. and Sahu, K. (2014). Role of natural products in drug discovery process. *Int. J. Drug Dev. Res.* 6: 172-204.

Siegel, R., Desantis, C., Virgo, K., Stein, K., Mariotto, A., Smith, T., Cooper, D., Gansler, T., Lerro, C. and Fedewa, S. (2012). Cancer treatment and survivorship statistics, 2012. *CA Cancer J. Clin.* 62: 220-241.

Single, A., Beetham, H., Telford, B. J., Guilford, P. and Chen, A. (2015). A comparison of real-time and endpoint cell viability assays for improved synthetic lethal drug validation. *J. Biomol. Screen*. 20: 1286-1293.

Sorice, A., Guerriero, E., Volpe, M. G., Capone, F., Cara, F. La, Ciliberto, G., Colonna, G. and Costantini, S. (2016). Differential response of two human breast cancer cell lines to the phenolic extract from flaxseed oil. *Molecules* 21: 319-337.

Su, Z., Yang, Z., Xie, L., Dewitt, J. P. and Chen, Y. (2016). Cancer therapy in the necroptosis era. *Cell Death Differ.* 23: 748-756.

Sung, H., Ferlay, J., Siegel, R. L., Laversanne, M., Soerjomataram, I., Jemal, A. and Bray, F. (2021). Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J. Clin.* 0: 1-41.

Tan, L. T.-H., Chan, C. K., Chan, K. G., Pusparajah, P., Khan, T. M., Ser, H. L., Lee, L. H. and Goh, B. H. (2019). *Streptomyces* sp. MUM256: a source for apoptosis inducing and cell cycle-arresting bioactive compounds against colon cancer cells. *Cancers* 11: 1742.

Tavangar, F., Sepehri, H., Jazi, M. S. and Asadi, J. (2017). Amphotericin B potentiates the anti-cancer activity of doxorubicin on the MCF-7 breast cancer cells. *J. Chem. Biol.* 10: 143-150.

Taylor, W. R. and Grabovich, A. (2009). Targeting the cell cycle to kill cancer cells. In *Pharmacology: Principles and Practice*, ed. M. Hacker, K. Bachmann, and W. Messer, pp. 429-453. The Netherlands: Elsevier Press.

Tedesco, P., Maida, I., Esposito, F. P., Tortorella, E., Subko, K., Ezeofor, C. C., Zhang, Y., Tabudravu, J., Jaspars, M., Fani, R. and Pascale, D. D. (2016). Antimicrobial activity of monoramnholipids produced by bacterial strains isolated from the Ross Sea (Antarctica). *Mar. Drugs* 14: 83.

Terao, Y., Nakamori, S. and Takagi, H. (2003). Gene dosage effect of L-proline biosynthetic enzymes on L-proline accumulation and freeze tolerance in *Saccharomyces cerevisiae*. *Appl. Environ. Microbiol*. 69: 6527-6532.

Thilakarathna, S. H. and Rupasinghe, H. P. V. (2013). Flavonoid bioavailability and attempts for bioavailability enhancement. *Nutrients* 5: 3367-3387.

Thomas, S. A. (2017). Chemotherapy agents that cause cardiotoxicity. *US Pharm.* 42: 24-33.

Thompson, A. M. and Moulder-Thompson, S. L. (2012). Neoadjuvant treatment of breast cancer. *Ann. Oncol.* 23: 231-236.

Thorat, B. R. (2018). Chemical extraction and biomedical importance of secondary organic metabolites from plants-a review. *J. Biomed. Ther. Sci.* 5: 9-42.

Tian, Y., Li, Y. and Zhao, F. (2017). Secondary metabolites from polar organisms. *Mar. Drugs* 15: 28.

Truong, J., Yan, A. T., Cramarossa, G. and Chan, K. K. (2014). Chemotherapy-induced cardiotoxicity: detection, prevention, and management. *Can. J. Cardiol.* 30: 869-878.

Tsai, I.-L., Kuo, T.-C., Ho, T.-J., Harn, Y.-C., Wang, S.-Y., Fu, W.-M., Kuo, C.-H. and Tseng, Y. J. (2013). Metabolomic dynamic analysis of hypoxia in MDA-MB-231 and the comparison with inferred metabolites from transcriptomics data. *Cancers* 5: 491-510.

Van Meerloo, J., Kaspers, G. J. and Cloos, J. (2011). Cell sensitivity assays: the MTT assay. *Methods Mol. Biol*. 731: 237-245.

Vanags, D. M., Porn-Ares, M. I., Coppola, S., Burgess, D. H. and Orrenius, S. (1996). Protease involvement in fodrin cleavage and phosphatidylserine exposure in apoptosis. *J. Biol. Chem*. 271: 31075-31085.

Vandenabeele, P., Galluzzi, L., Vanden Berghe, T. and Kroemer, G. (2010). Molecular mechanisms of necroptosis: an ordered cellular explosion. *Nat. Rev.*

Mol. Cell Biol. 11: 700-714.

Vanitallie, T. B. and Nufert, T. H. (2003). Ketones: metabolism's ugly duckling. *Nutr. Rev.* 61: 327-341.

Vazquez-Rivera, D., Gonzalez, O., Guzman-Rodriguez, J., Diaz-Perez, A. L., Ochoa-Zarzosa, A., Lopez-Bucio, J., Meza-Carmen, V. and Campos-Garcia, J. (2015). Cytotoxicity of cyclodipeptides from *Pseudomonas aeruginosa* PAO1 leads to apoptosis in human cancer cell lines. *BioMed Res. Int*. 2015: 197608.

Vermeulen, K., Bockstaele, D. R. V. and Berneman, Z. N. (2003). The cell cycle: a review of regulation, deregulation and therapeutic targets in cancer. *Cell Prolif.* 36: 131-149.

Vior, N. M., Lacret, R., Chandra, G., Dorai-Raj, S., Trick, M. and Truman, A. W. (2018). Discovery and biosynthesis of the antibiotic bicyclomycin in distantly related bacterial classes. *Appl. Environ. Microbiol*. 84: 02828-02817.

Volkova, M. and Russell, R. (2011). Anthracycline cardiotoxicity: prevalence, pathogenesis and treatment. *Curr. Cardiol. Rev.* 7: 214-220.

Wall, P. E. (2000). Chromatography: thin-layer planar/spray reagents. In *Encyclopedia of Separation Science*, ed. I. D. Wilson, pp. 907-915. New York: Academic Press.

Wander, S. A., Hennessy, B. T. and Slingerland, J. M. (2011). Next-generation mTOR inhibitors in clinical oncology: how pathway complexity informs therapeutic strategy. *J. Clin. Invest.* 121: 1231-1241.

Wang, Z., Wang, N., Chen, J. and Shen, J. (2012). Emerging glycolysis targeting and drug discovery from Chinese medicine in cancer therapy. *Evid. Based Complement. Alternat. Med.* 2012: 873175.

Warburg, O., Wind, F. and Negelein, E. (1926). The metabolism of tumours in the body. *J. Gen. Physiol*. 8: 519-530.

Ward, P. S. and Thompson, C. B. (2013). Metabolic reprogramming: a cancer hallmark even Warburg did not anticipate. *Cancer Cell* 21: 297-308.

Waseem, M., Bhardwaj, M., Tabassum, H., Raisuddin, S. and Parvez, S. (2015). Cisplatin hepatotoxicity mediated by mitochondrial stress. *Drug Chem. Toxicol.* 38: 452-459.

Werdyani, S., Wijayanti, N., Fitria, A. and Rahmawati, S. (2017). Cytotoxic effects of ethyl acetate extract from secondary metabolites of *Streptomyces* sp. GMY01 on human breast cancer MCF-7 cell line. *Asian J. Pharm. Clin. Res.* 10: 5.

Williams, G. H. and Stoeber, K. (2012). The cell cycle and cancer. *J. Pathol.* 226: 352-364.

Wise, D. R. and Thompson, C. B. (2011). Glutamine addiction: a new therapeutic target in cancer. *Trends Biochem. Sci*. 35: 427-433.

Wu, J. and Yan, L. J. (2015). Streptozotocin-induced type 1 diabetes in rodents as a model for studying mitochondrial mechanisms of diabetic beta cell glucotoxicity. *Diabetes Metab. Syndr. Obes.* 8: 181-188.

Xintaropoulou, C., Ward, C., Wise, A., Marston, H., Turnbull, A. and Langdon, S. P. (2015). A comparative analysis of inhibitors of the glycolysis pathway in breast and ovarian cancer cell line models. *Oncotarget* 6: 25677-25695.

Xu, R.-H., Pelicano, H., Zhou, Y., Carew, J. S., Feng, L., Bhalla, K. N., Keating, M. J. and Huang, P. (2005). Inhibition of glycolysis in cancer cells: a novel strategy to overcome drug resistance associated with mitochondrial respiratory defect and hypoxia. *Cancer Res*. 65: 613-622.

Yan, G., Du, Q., Wei, X., Miozzi, J., Kang, C., Wang, J., Han, X., Pan, J., Xie, H., Chen, J. and Zhang, W. (2018). Application of real-time cell electronic analysis system in modern pharmaceutical evaluation and analysis. *Molecules* 23: 3280.

Yang, A., Si, L., Shi, Z., Tian, L., Liu, D., Zhou, D., Prokch, P. and Lin, W. (2013). Nitrosporeusines A and B, unprecedented thioester-bearing alkaloids from the Arctic *Streptomyces nitrosporeus*. *Org. Lett*. 15: 5366-5369.

Yang, C., Ko, B., Hensley, C. T., Jiang, L., Wasti, A. T., Kim, J., Sudderth, J., Calvaruso, M. A., Lumata, L., Mitsche, M., Rutter, J., Merritt, M. E. and DeBerardinis, R. J. (2014). Glutamine oxidation maintains the TCA cycle and cell survival during impaired mitochondrial pyruvate transport. *Mol. Cell* 56: 414-424.

Yang, S., Zhou, Q. and Yang, X. (2007). Caspase-3 status is a determinant of the differential responses to genistein between MDA-MB-231 and MCF-7 breast cancer cells. *Biochim. Biophys. Acta* 1773: 903-911.

Yang, Z. J., Chee, C. E., Huang, S. and Sinicrope, F. A. (2011). The role of autophagy in cancer: therapeutic implications. *Mol. Cancer Ther.* 10: 1533-1541.

Yin, J., Ren, W., Huang, X., Deng, J., Li, T. and Yin, Y. (2018). Potential mechanisms connecting purine metabolism and cancer therapy. *Front. Immunol.* 9:1697.

Yip, K. W. and Reed, J. C. (2008). Bcl-2 family proteins and cancer. *Oncogene* 27: 6398-6406.

Yip, W. K., Cheenpracha, S., Chang, L. C., Ho, C. C. and Seow, H. F. (2010). Anti-proliferative and anti-invasive properties of a purified fraction from *Streptomyces sp.* H7372. *Int. J. Oncol*. 37: 1229-1241.

Yoshimi, N., Futamura, T., Kakumoto, K., Salehi, A. M., Sellgren, C. M., Holmen-larsson, J., Jakobsson, J., Palsson, E., Landen, M. and Hashimoto, K. (2016). Blood metabolomics analysis identifies abnormalities in the citric acid cycle,

urea cycle, and amino acid metabolism in bipolar disorder. *BBA Clin*. 5: 151-158.

Yu, X., Deng, Q., Bode, A. M., Dong, Z. and Cao, Y. (2013). The role of necroptosis, an alternative form of cell death, in cancer therapy. *Expert Rev. Anti-cancer Ther.* 13: 883-893.

Yu, J., Zhang, L., Liu, Q., Qi, X., Ji, Y. and Kim, B. S. (2015). Isolation and characterization of actinobacteria from Yalujiang coastal wetland, North China. *Asian Pac. J. Trop. Biomed.* 5: 555-560.

Yuneva, M., Zamboni, N., Oefner, P., Sachidanandam, R. and Lazebnik, Y. (2007). Deficiency in glutamine but not glucose induces MYC-dependent apoptosis in human cells. *The J. Cell Bio*. 178: 93-105.

Zigon, P., Mrak-Poljsak, K., Lakota, K., Tercelj, M., Cucnik, S., Tomsic, M. and Sodin-Semrl, S. (2016). Metabolic fingerprints of human primary endothelial and fibroblast cells. *Metabolomics* 12: 92.

Zhang, H., Saurav, K., Yu, Z., Mandi, A., Kurtan, T., Li, J., Tian, X., Zhang, Q., Zhang, W. and Zhang, C. (2016). α-Pyrones with diverse hydroxy substitutions from three marine-derived *Nocardiopsis* strains. *J. Nat. Prod.* 79: 1610-1618.

Zhang, X., Ye, X., Chai, W., Lian, X.-Y. and Zhang, Z. (2016). New metabolites and bioactive actinomycins from marine-derived *Streptomyces* sp. ZZ338. *Mar. Drugs* 14: 1-9.

Zhao, Y., Liu, H., Liu, Z., Ding, Y., Ledoux, S. P., Wilson, G. L., Voellmy, R., Lin, Y., Lin, W., Nahta, R., Liu, B., Fodstad, O., Chen, J., Wu, Y., Price, J. E. and Tan, M. (2012). Overcoming Trastuzumab resistance in breast cancer by targeting dysregulated glucose metabolism. *Cancer Res*. 71: 4585-4597.

Zheng, S., Zhou, S., Qiao, G., Yang, Q., Zhang, Z., Lin, F., Min, D., Tang, L., Li, H., Sun, Y., Zhao, H., Shen, Z. and Yao, Y. (2015). Pirarubicin-based chemotherapy displayed better clinical outcomes and lower toxicity than did doxorubicin-based chemotherapy in the treatment of non-metastatic extremity osteosarcoma. *Am. J. Cancer Res.* 5: 411-422.

Zolfaghari, B., Jafarian, A. and Rezaei, M. (2018). Evaluation of cytotoxic effect of different extracts of *Seidlitzia rosmarinus* on HeLa and HepG2 cell lines. *Adv. Biomed. Res.* 7: 132.

BIODATA OF STUDENT

Yeoh Chiann Ying was born in Pulau Pinang, Malaysia in 1988. She received her primary education from Sekolah Rendah Jenis Kebangsaan (C) Kim Sen, and continued her secondary education in Sekolah Menengah Kebangsaan Bukit Mertajam, Pulau Pinang. She then did her Form Six in Sekolah Menengah Kebangsaan Tinggi Bukit Mertajam, Pulau Pinang. The student obtained her first degree in Bachelor of Science (Biological Sciences) from Universiti Terengganu Malaysia in 2011. Her passion towards scientific research has motivated her to pursue her Master of Science (MSc) at the Institute for Research in Molecular Medicine (INFORMM), Health Campus, Universiti Sains Malaysia, Kelantan. She was also appointed as research assistant at INFORMM, USM (2011 – 2014). In year 2015, she was accepted to further her Doctor of Philosophy (PhD) study in University Putra Malaysia. The postgraduate academia had given her the opportunity to acquire knowledges and skills in carrying out research works, especially in the field of molecular diagnostics and natural product based-drug discovery. She was also a recipient of MyBrain15 Scholarship during her postgraduate studies.

LIST OF PUBLICATIONS

Journal articles

Yeoh, C. Y., Rosandy, A. R., Khalid, R. M. and Cheah, Y. K. (2021). Cytotoxicity of ethyl acetate extract from a novel actinobacteria, *Barrientosiimonas humi* via induction of apoptosis, cell cycle arrest and caspase pathway in breast cancer cells. *Asian Pacific Journal of Tropical Biomedicine* (Submitted and under peer review).

Yeoh, C. Y. and Cheah, Y. K. (2020). Bioinformatics in the identification of microorganisms. *Life Sciences, Medicine and Biomedicine* 9(4): 64.

Rosandy, A. R., **Yeoh, C. Y**., Cheah, Y. K., Bakar, M. A., Muhammad, A. and Khalid, R. M. (2019). Psychrotolerant actinobacteria *Barrientosiimonas humi* 39^T as a source of diketopiperazine. *Malaysian Journal of Analytical Sciences*, 4(23): 748-762.

Rosandy, A. R., **Yeoh, C. Y**., Cheah, Y. K., Lim, S. J., Latip, J., Murad, A. M. A., Bakar, M. A. and Khalid, R. M. (2018). (-)-Glaciantarcin a new dipeptide and some secondary metabolites from the psychrophilic yeast *Glaciozyma antarctica* P112. *Sains Malaysiana* 47(11).

Proceedings/Abstracts

Yeoh, C. Y., Khalid, R. M., Rosandy, A. R. and Cheah, Y. K. (2017). Phenotype microarray profiling of the cytotoxic activity of a novel actinobacteria, *Barrientosiimonas humi* on MDA-MB-231 breast cancer cells. Mini Symposium of Phenotypic Microarray, Faculty of Medicine and Health Sciences, UPM, Malaysia (6^{th}-7^{th} September 2017).

Yeoh, C. Y., Lee, S. L., Khalid, R. M., Rosandy, A. R., Khoo, C. H. and Cheah, Y. K. (2016). The study of anti-cancer properties of bioactive fractions produced by a novel Antarctica actinobacteria, *Barrientosiimonas humi*. The 7^{th} SCAR Open Science Conference, KLCC Convention Centre, Malaysia (22^{nd}-26^{th} August 2016).

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