UNIVERSITI PUTRA MALAYSIA

ANTI-PROLIFERATIVE AND APOPTOSIS INDUCTION EFFECTS OF Anacardium occidentale L. AND Morinda citrifolia L. SHOOT EXTRACTS ON BREAST, LIVER, AND COLORECTAL CANCER CELLS

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Anacardium occidentale or also known as cashew and *Morinda citrifolia* or also known as noni are popular traditional plants among Malaysian community. The shoots of these plants are commonly consumed raw or blanched as side dishes or '*ulam*' during meal times. Aside from shoots, other parts of the plants are also consumed in traditional medicines for the prevention and treatment of various diseases. Most of the study was focused on the fruit part of the plant and some of the study that used the plant leaves extracted with different types of solvents. Besides, the selected types of cancer was chosen as these three cancers were on top ten of most common cancer among Malaysian and there is limited study of cashew and noni against these cancer types. As cancer is one of the most leading cause of death in Malaysia, this study was aimed to determine the anti-proliferative effects of cashew and noni shoots in various types of cancer cell lines. Both shoots of cashew and noni were obtained from Taman Herba, Universiti Putra Malaysia and the freeze-dried samples were extracted with 70 % (v/v) ethanol. The selected cancer cell lines were breast cancer (MDA-MB-231) cells, liver cancer (HepG2) cells and colorectal cancer (HT-29) cells. The cells were treated with extracts of cashew and noni shoots for cytotoxicity test using (3-(4,5-dimethylthiazol-2-yl)-2,5 diphenyltetrazolium bromide) (MTT) assay. The results showed that cashew shoot extract had IC_{50} of 81.10 µg/ml, 307.50 µg/ml and 272.60 µg/ml against MDA-MB-231, HepG2 and HT-29 cells, respectively. Noni shoot extract showed IC_{50} of 49.72 µg/ml, 307.5 µg/ml and 65.43 µg/ml against MDA-MB-231, HepG2 and HT-29 cells, respectively. The MTT result also showed that both of the extract had no sign of cytotoxicity towards normal mouse fibroblast (BALB/c 3T3) cells. The extracts that demonstrated the IC_{50} value below 100 µg/ml were selected for further determination of apoptosis response using acridine orange (AO)/ propidium iodide (PI) dual fluorescent assay. The selected cancer cell lines were treated with extracts of cashew and noni shoots for 24, 48, and 72 hours of incubations and stained with nuclear staining dye which is acridine orange and propidium iodide and observed using

fluorescence microscope. The results showed typical sign of apoptosis such as chromatin condensation, nuclear fragmentation and cell blebbing were markedly induced in all treated-cancer cells with cashew and noni shoots extracts after 24, 48 and 72 hours in time-dependent manner. In addition, the selected cancer cell lines were further analyzed for the determination of cell cycle progression using propidium iodide dye and flow cytometer. The data was analyzed using one-way analysis of variance (ANOVA) with Tukey's post hoc test. The breast cancer cells were treated with three different concentrations of cashew (40 µg/ml, 80 µg/ml, and 120 µg/ml) and noni extract (25 µg/ml, 50 µg/ml, and 75 µg/ml) for 72 hours of incubation. As for colorectal cancer cells were treated with noni extract (33 µg/ml, 65 µg/ml and 98 µg/ml) for 72 hours. The results from cell cycle analysis showed significant increase in subG_0 phase indicating apoptosis and significant decrease in G_0/G_1 phase in a dose-dependent manner. The cashew and noni ethanolic shoots extracts possessed potential anti-cancer properties, thereby gas chromatography mass spectrometry (GCMS) were carried out to characterize the active compounds in both plants. It was found that cashew shoot extract are abundant with sitosterol, tannin, pyrogallol, and phenol. As for noni shoot extract, they contained acetic acid and ethriol. In summary, both of the extracts showed cytotoxicity towards selected cancer cells and have the potential to be the studied further to understand underlying mechanism of the cashew and noni extracts in cancer cell lines and possibility to be developed as nutraceutical or functional food products.

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

KESAN ANTI-PROLIFERATIF DAN INDUKSI APOPTOSIS PUCUK *Anacardium occidentale* L. DAN *Morinda citrifolia* L. TERHADAP SEL KANSER PAYUDARA, HATI, DAN KOLOREKTAL

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Anacardium occidentale adalah lebih dikenali sebagai gajus dan *Morinda citrifolia* yang dikenali sebagai mengkudu adalah tumbuhan tradisional yang popular di kalangan rakyat Malaysia. Pucuk kedua-dua tanaman ini selalunya dimakan bersama makanan utama sama ada secara mentah atau dicelur. Selain pucuk, bahagian lain tumbuhan ini juga digunakan dalam perubatan tradisional untuk merawat pelbagai penyakit. Memandangkan kanser merupakan salah satu penyebab kematian utama di Malaysia, objektif penyelidikan ini adalah untuk menentukan kesan anti-proliferatif dan memberi maklumat tentang sifat anti-kanser yang terdapat di dalam pucuk gajus dan mengkudu. Kedua-dua pucuk tanaman ini diperoleh daripada Taman Botani, Universiti Putra Malaysia dan sampel tersebut kemudian diekstrak dengan menggunakan 70 % etanol selepas dibeku kering. Sel kanser yang terpilih adalah sel kaser payudara (MDA-MB-231), sel kanser hati (HepG2) dan sel kanser kolorektal (HT-29) dan semua sel tersebut dirawat bersama ekstrak pucuk gajus dan mengkudu menggunakan asai MTT. Keputusan asai tersebut menunjukkan esktrak pucuk gajus mempunyai nilai IC_{50} 81.1 µg/ml terhadap sel MDA-MB-231, 307.5 µg/ml terhadap sel HepG2 dan 272.6 µg/ml terhadap sel HT-29. Manakala ekstrak pucuk mengkudu menunjukkan nilai IC_{50} 49.72 µg/ml terhadap sel MDA-MB-231, 307.50 µg/ml terhadap sel HepG2 dan 65.43 µg/ml terhadap sel HT-29. Berdasarkan keputusan asai MTT, nilai IC_{50} yg rendah daripada 100 µg/ml dipilih untuk dijalankan ujian selanjutnya menggunakan asai dual pendarflour AO/PI. Sel kanser yang terpilih dirawat dengan ekstrak pucuk gajus dan mengkudu selama 24, 48, dan 72 jam. Keputusan asai ini menunjukkan esktrak pucuk gajus dan mengkudu mendorong sel kanser terhadap kematian sel secara terkawal (apoptosis) selari dengan masa rawatan di mana morfologi menunjukkan tanda-tanda apoptosis seperti pemeluwapan nukleus, rekahan DNA dan sel mengembung dan mengecut. Selepas asai AO/PI, sel kanser payudara dirawat dengan ekstrak pucuk gajus pada kepekatan 40 µg/ml, 80 µg/ml dan 120 µg/ml manakala ekstrak pucuk mengkudu pada kepekatan 25 µg/ml , 50 µg/ml dan 75 µg/ml selama 72 jam. Sel kanser kolorektal dirawat hanya dengan

ekstrak pucuk mengkudu pada kepekatan 33 µg/ml, 65 µg/ml, dan 98 µg/ml selama 72 jam. Keputusan analisa tersebut menunjukkan sel di dalam fasa subG_0 meningkat secara ketara menandakan terdapat apoptosis dan sel di dalam fasa G_0/G_1 menurun secara ketara. Ini menunjukkan ekstrak pucuk gajus dan menkudu yang dirawat menyebabkan apoptosis terhadap sel kanser yang dirawat. Ekstrak pucuk gajus dan mengkudu menunjukkan keupayaan anti-kanser, oleh itu kromatografi gas spektrometri jisim (GC/MS) telah dijalankan untuk mengenalpasti bahan aktif yang terdapat di dalam ekstrak etanol pucuk gajus dan mengkudu. Didapati bahawa ekstrak gajus banyak terdapat dengan sitosterol, tanin, pyrogallol, dan fenol. Bagi ekstrak pucuk mengkudu, ia mengandungi asid asetik dan etriol. Sebagai rumusan, kedua-dua ekstrak menpunyai potensi untuk dikaji lebih mendalam untuk memahami mekanisme ekstrak gajus dan mengkudu tersebut terhadap sel kanser terpilih dan mempunyai potensi untuk dibangunkan sebagai produk nutraseutikal dan makanan berfungsi.

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

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LIST OF ABBREVIATIONS

%	Percentage
^{O}C	Degree Celsius
µg	Microgram
µL	Microlitre
ANOVA	Analysis of Variance
AO	Acridine Orange
ATCC	American Type Culture Collection
BALB/c 3T3	Normal Mouse Fibroblast
CDK	Cyclin Dependent Kinase
CO_2	Carbon Dioxide
DMSO	Dimethy Sulfoxide
DNA	Deoxyribonucleic acid
ELISA	Enzyme-linked Immunosorbent Assay
FACS	Fluorescence-activated cell sorting
FBS	Fetal bovine serum
G_0	Resting phase
G_1	Gap 1 phase
G_2	Gap 2 phase
GCMS	Gas chromatography mass spectrophotometry
HepG2	Hepatocellular liver
HPLC	High performance liquid chromatography
HT-29	Colorectal cancer
IC_{50}	Inhibitory concentration for 50 %
MDA-MB-231	Human breast cancer
mg	Miligram
ml	Mililitre
MOH	Ministry of Health
MTT	3-(4, 5-dimethythiazol-2-yl)-2, 5-diphenyltetrazolium bromide
PI	Propidium iodide
RNase	Ribonuclease
RPMI	Roswell Park Memorial Institute
S	Synthesis phase
SD	Standard Deviation
SPSS	Statistical Package for the Social Sciences
WHO	World Health Organization

CHAPTER 1

INTRODUCTION

1.1 Background of research

Cancer is a major public health problem worldwide and it is leading cause of death in both more and less developed countries (Torre, Siegel, Ward, & Jemal, 2016). With the existing burden, it is estimated that number of cases and death of cancer will be increased rapidly as the population grows and aging plus with the adoption of behavior that increase the risk of getting cancer such as tobacco use, alcohol consumption, physical inactivity, and excess body weight (Torre et al., 2016). It is also estimated that over 20 million new cases will be expected annually by as early as 2025 (Bray, 2014).

Plant has been used for hundred years for treating various disease (Kim, Park, Lee, Seo, & Kim, 2015). It is reported that some of medicinal plants possess anti-cancer activity and polyphenols from fruits and vegetables are responsible molecule for chemo preventive effects (Mutalib, Ali, Othman, Ramasamy, & Rahmat, 2016). Plant-derived material possess highly diverse and complex molecular structures compared to synthetic drugs and play an important role in human health and in the development of new anticancer drugs (Faezizadeh, Gharib, & Godarzee, 2016). Besides, plant used in traditional medicines has been accepted as an alternative for therapeutic drug development in modern medicine (Vijayarathna & Sasidharan, 2012).

In Malaysia, there are group of traditional Malaysian vegetables known as *ulam* and they are consumed in raw or boiled form usually with rice-based meal (Bachok, Yusof, Ismail, & Hamid, 2014). *Ulam* can be defined as fresh green salad that tossed in a blend of fermented sauce, aromatic herbs or spices and eaten especially by Malays as a side dishes with rice (Reihani & Azhar, 2012). Among many of the plants that used as *ulam* by the Malaysian community, cashew and noni shoots are example of popular plant that preferred as an accompaniment to their meal. There are many nutritional studies that shows the benefits of cashew and noni plant but most of the studies focus on the other parts of the plant that includes fruits, stem, bark, and roots.

1.2 Problem statement

According to Malaysian National Cancer Registry Report 2016, cancer has become top leading cause of mortality in the country and the top leading cancers among Malaysian populations includes breast, colorectal, and liver cancers (Azizah, Norsaleha, Hashimah, Asmah, & Mastulu, 2016). This situations cause a burden to

the health care system as the cost for the treatment for cancers are huge. Moreover, current cancer therapy such as chemotherapy and radiation therapy can causes serious side effects such as nausea, anemia, and hair loss to patients

Thus, most people try to find alternative ways to either replace or complement the modern medicines for the treatment of cancer. This makes the focus on herbal and plant products as an alternative for cancer treatment increase. Malaysian people has been use plants as a part in traditional medicine from a long time ago to treat various disease and conditions.

Shoots of cashew and noni plant were a well-known vegetables and herbs among Malaysian community and they always consumed with main meal. With the further research about the anti-cancer properties of both of the herbs, the findings can provide basic information about the potential of medicinal properties of the herbs and perhaps the data can be used in developing an alternative food that gives health benefits to community as general and to cancer patients specifically.

1.3 Significance of study

In the daily life nowadays, there are many situations that contribute to the formation of the free radical in the body such as during stress condition, metabolism process, cigarettes smoke, air pollution, alcohol intake as well as the exposure to the sunlight. When the production free radical exceeds the antioxidant capacity of the body system, it will lead to oxidative stress (Zima et al., 2001). Oxidative stress is reported to be responsible for the development of many disease including heart disease, cancer, as well as neurodegenerative disease (Astley, 2003)

With the increasing trends of cancer incidence each year, in order to reduce the public health burden of cancer, more research for more effective cancer treatment and free of any side effects to the patient. One of the efforts is through the changes in dietary intake by looking for natural resources that possess anti-cancer properties. Furthermore, the current treatment for cancer including radiotherapy, chemotherapy and drugs gives the unwanted side effects to cancer patients. Hence, the focus on natural products such as plants sources as a potential food to provide the alternative ways for the cancer patients to reduce their burden.

Moreover, the approach trough diet therapy can increase the public awareness about the importance of healthy food intake especially fruits and vegetables in order to reduce the risk of getting chronic disease such as cancer not only for treatment but also for prevention purpose.

1.4 Objectives

1.4.1 General objective

To study the anti-proliferative and apoptosis induction effects of extracts from cashew and noni shoots in selected cancer cell lines.

1.4.2 Specific objectives

1. To determine and compare anti-proliferative effect of cashew and noni shoots extracts in human breast cancer (MDA-MB-231), human carcinoma cell line (HepG2) and human colon cancer cell line (HT-29) cells using MTT assay.

2. To determine and compare apoptosis induction effects of cashew and noni shoots extracts in human breast cancer (MDA-MB-231), human carcinoma cell line (HepG2) and human colon cancer cell line (HT-29) cells using AO/PI dual fluorescent assay.
3. To determine and compare cell cycle analysis of cashew and noni shoots extracts in human breast cancer (MDA-MB-231), human carcinoma cell line (HepG2) and human colon cancer cell line (HT-29) cells using flow cytometry.

4. To determine phytochemicals in the 70% ethanol extracts of cashew and noni shoots using GCMS analysis.

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LIST OF PUBLICATIONS

Mohd Amir Ashraf Meli, Nurul Husna Shafie, Su Peng Loh, & Asmah Rahmat (2017). Anti-proliferative and Apoptosis Induction Effects of Cashew Shoot Extract in Breast Cancer Cells. Malaysian Journal of Medicine and Health Sciences 13 (Supplement 1):21.

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