SCREENING OF PHYTOCHEMICAL AND ANTI-PROLIFERATIVE EFFECT OF *Anacardium occidentale* L. SHOOT EXTRACT AGAINST BREAST, LIVER AND COLORECTAL CANCER CELLS

By

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ABSTRACT

Anacardium occidentale also known as cashew are popular traditional food among Malaysian community. The cashew shoots are typically consumed raw or half boil as side dishes or *ulam* during meal times. Cancer is one of the most leading causes of death and has become a significant public health issue in Malaysia. Herbs and plants contain phytonutrients that exhibit various medicinal properties and traditionally treat various diseases have given rise to interest in traditional medicine and cultural medicine. In this study, we aim to study the phytochemical screening and anti-proliferative effect of cashew shoots against breast, liver and colorectal cancer cells. The breast cancer (MDA-MB-231), liver cancer (HepG2), and colorectal cancer (HT-29) cell lines were treated with 70% ethanol extract of cashew shoot for cytotoxicity test with 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. Apoptosis induction effects were determined from cell cycle analysis using flow cytometry. Phytochemical compound screening of cashew shoot extract was carried out by using liquid chromatography mass spectrometry (lcms). The cytotoxicity assay showed that cashew shoot extract had IC_{50} of 81.1 μg/ml, 307.5 μg/ml and 272.6 μg/ml against MDA-MB-231, HepG2 and HT-29 cell lines respectively. Apoptosis induction by cashew shoot extract was demonstrated with a significant increase of cell count in sub G_0 phase for 40 μg/ml at 21.83 ± 6.22 %, 80 μg/ml at 50.66 ± 4.30 %, 120 μg/ml at 75.81 ± 4.97 % compared to control at 5.60 ± 2.14 %, and significant decrease in subsequent phases in MDA-MB-231 cell lines in cell cycle analysis. Several compounds with anticancer activity includes citric acid, gallic acid, myricetin and hinokiflavone were identified in cashew shoot extract by LCMS. These findings showed the potential anticancer properties of cashew shoot extract towards breast cancer cells. Thus, further study is needed to investigate the mechanism of cashew shoot as anticancer agent.

ABSTRAK

Anacardium occidentale adalah dikenali sebagai gajus merupakan makanan tradisional yang popular di kalangan masyarakat Malaysia. Pucuk gajus biasanya dimakan secara mentah atau dicelur sebagai ulam. Kanser merupakan salah satu penyebab kematian utama dan telah menjadi isu kesihatan awam yang penting di Malaysia. Herba dan tumbuhan mengandungi unsur khasiat tumbuhan yang mempamerkan pelbagai khasiat perubatan dan merawat pelbagai penyakit secara tradisional telah menimbulkan minat terhadap perubatan tradisional dan perubatan budaya. Objektif kajian ini adalah untuk mengkaji pemeriksaan unsur khasiat tumbuhan dan kesan anti-proliferatif pucuk gajus terhadap sel-sel kanser payudara, hati dan kolorektal. Sel kanser payudara (MDA-MB-231), sel kanser hati (HepG2), dan sel kanser kolorektal (HT-29) telah dirawat bersama dengan 70 % ekstrak etanol pucuk gajus untuk ujian sifat antikanser dengan asai 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT). Kesan induksi apoptosis ditentukan dengan analisis kitaran sel menggunakan sitometri aliran. Pemeriksaan unsur khasiat tumbuhan ekstrak pucuk gajus telah dijalankan dengan menggunakan spektrometri jisim kromatografi cecair (lcms). Ujian asai MTT menunjukkan bahawa ekstrak pucuk gajus mempunyai IC_{50} 81.1 µg/ml, 307.5 µg/ml dan 272.6 µg/ml terhadap MDA-MB-231, HepG2 dan HT-29 masing-masing. Induksi apoptosis oleh ekstrak pucuk gajus telah ditunjukkan dengan peningkatan bilangan sel secara ketara dalam fasa sub G_0 dengan 40 µg/ml pada 21.83 ± 6.22 %, 80 µg/ml pada 50.66 ± 4.30 %, 120 µg/ml pada 75.81 ± 4.97 % berbanding dengan kawalan dengan 5.60 ± 2.14 %, dan penurunan ketara dalam fasa berikutnya dalam sel MDA-MB-231 dalam analisis kitaran sel. Beberapa sebatian dengan aktiviti antikanser termasuk asid sitrik, asid gallic, miricetin dan hinokiflavon telah dikenal pasti dalam ekstrak pucuk gajus oleh LCMS. Keputusan ini menunjukkan potensi sifat antikanser ekstrak pucuk gajus kepada sel-sel kanser payudara. Oleh itu, kajian lanjut diperlukan untuk menyiasat mekanisme pucuk gajus sebagai agen antikanser.

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LIST OF ABBREVIATIONS

%	Percent
°C	Degree Celsius
µg	Microgram
µL	Microlitre
ALDH	Aldehyde Dehydrogenase
APAF-1	Apoptotic protease- activating factor-1
ANOVA	Analysis of Variance
ATCC	American Type Culture Collection
BAK	BCL-2 homologous antagonist killer
BAX	BCL-2- associated X protein
BALB/3T3	Normal Mouse Fibroblast
BCL-2	B-cell lymphoma 2
BRCA1	Breast Cancer Gene 1
BRCA2	Breast Cancer Gene 2
CDK	Cyclin Dependent Kinase
CO_2	Carbon Dioxide
DED	death effector domain
DISC	death-inducing signalling complex
DMSO	Dimethyl Sulfoxide
DNA	Deoxyribonucleic acid
EGCG	Epigallocatechin gallate
ELISA	Enzyme-linked Immunosorbent Assay
ERα	estrogen receptor alpha
FADD	Fas-associated death domain
TRADD	TNF receptor- associated death domain
FACS	Fluorescence-activated cell sorting
FBS	Foetal bovine serum
G_0	Resting phase
G_1	Gap 1 phase
G_2	Gap 2 phase
HDI	Human Development Index
HepG2	Hepatocellular liver
HPLC	High Pressure Liquid Chromatography
HT-29	Colorectal cancer
IAP	inhibitor of apoptosis proteins
IC_{50}	Inhibitory concentration for 50 %
LCMS	Liquid chromatography mass spectrometry
MDA-MB-231	Human breast cancer
mg	Miligram
ml	Mililitre
MOH	Ministry of Health
MOMP	Mitochondrial outer membrane permeabilization
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
NCI	National Cancer Institute
NHMS	National Health and Morbidity Survey
NIH	National Institute of Health
RNase	Ribonuclease

RPMI	Roswell Park Memorial Institute
S	Synthesis phase
SD	Standard Deviation
SMAC	second mitochondria-derived activator of caspase
SPSS	Statistical Package for the Social Sciences
WHO	World Health Organization
XIAP	X-linked inhibitor of apoptosis protein

CHAPTER 1

INTRODUCTION

1.1 Background of Research

Cancer has become a significant public health issue and among the commonest causes of death worldwide, with numerous people are diagnosed and more than half the mortality rate (Ma & Yu, 2006). Despite substantial progress that has been made in the past few years regarding prevention and treatment options for different cancers, the cancer burden is rising due to the population growing and aging in addition to lifestyle risks, including dietary habits, obesity and alcohol consumption (Fitzmaurice et al., 2015). It is predicted that the new cancer incidence will be over 20 million annually by 2025 (Bray, 2014). According to the epidemiology trend for the leading cause of mortality from 2016 to 2060, expected by WHO, the cancer mortality rate will increase 2.08-fold by 2060. Until then, malignancies will become the most common cause of mortality worldwide by as early as 2030 (Mattiuzzi & Lippi, 2019).

Briefly, cancer is defined as the quick formation of a cell anomaly that grows into a tumour and it would be breast cancer if the tumour were in the breast tissues. Among all the cancer types, breast cancer has the highest cancer incidence and the highest cause of mortality and morbidity among women worldwide (Becker, 2015). According to Malaysia National Cancer Registry Report 2012 – 2016, breast cancer has the highest cancer incidencein Malaysia and has remained its crown since 2007. In addition, it is also the most common cancer among female (Azizah et al., 2019) and have seen an increasing trend among young female (Tan et al., 2020). Meanwhile, colorectal cancer is the commonest cancer among Malaysian males and the second commonest cancer among Malaysian females (Azizah et al., 2019). Accordingto GLOBOCAN 2018, it ranks third commonest cause of cancer deaths in Malaysia (Bray et al., 2018). Briefly, colorectal cancer can also be colon or bowel cancer. Generally,the mutation of these cells leads to uncontrolled proliferation and growth that lead to the formation of a tumour that stems from the cell lining of the large intestine and or rectum and eventually the formation of colorectal cancer. Besides, liver cancer was reported as the top 5 most frequent cancer in both males and females, with 3rd in overall cancer mortality. The major forms of primary liver cancer are hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (iCCA) that grow against the background of liver diseases such as cirrhosis, non-alcholic fatty liver disease, chronic liver damage and fibrosis (Castelli, Pelosi & Testa, 2018).

Herbs and plants contain phytonutrients that exhibit various medicinal properties and traditionally treat various diseases (Kim et al., 2015). It has given rise to interest in traditional medicine and cultural medicine. Some of the plants extract from different parts such as roots, stems and leaves that have been used widely for the treatment of infectious disease, inflammation and oxidative stress-related conditions (Olajide, Aderogba & Fiebich, 2013). In addition, the polyphenols from fruits and vegetables exhibit chemo-preventive effects that are reported to exhibit anticancer activity (Mutalib et al., 2016).

Traditional medicinal plants can synthesize a great mixture of chemical compounds used as therapeutic remedies. Furthermore, they can be used as an alternative source for western medicine as they are inexpensive and natural(Onuh et al., 2017). Therefore, the utilisation of plants as traditional medicines has been involved as therapeutic drug development in modern medicine (Vijayarathna & Sasidharan, 2012).

Cashew shoots are examples of *ulam* that is widely consumed among the Malaysian community. Different part of the cashew plant is comprised of different nutrients, for example, cashew nut shells contain anacardic acid, cardanol, cardol for industry application, cashew apple contains gallic acid, myricetin, quercetin, cashew leaf contains quercetin as dominant flavonoid and chlorogenic acid as the dominant phenolic acid, cashew nuts are rich in unsaturated fatty acids such as linolenic and oleic acid, while the cashew shoot contains polyphenol and flavonoids (Salehi et al., 2020; Chan et al., 2017). Although cashew has been studied extensively, most of the studies focus on other parts of the plant, for instance, nuts, fruits, leaves and bark, for antibacterial, anti-fungal, antioxidant and anti-inflammatory properties (Gomes Junior et al., 2020; Salehi et al., 2020). Therefore, further studies on the phytonutrients in cashew roots can contribute to the overall benefits of cashew.

1.2 Problem Statement

According to GLOBOCAN 2018, the cancer incidence in Malaysia is predicted to be doubled by 2040, which is from 43,837 to 84,158 cancer cases (Bray et al., 2018). While it is undeniable that cancer is a major health risk in Malaysia, another report from Malaysian National Cancer Registry in 2016 highlighted that cancer had become the highest cause of mortality, with breast and colorectal being the commonest cancers among Malaysian populations (Azizah et al., 2019). It is widely known that the cost for cancer treatment is paramount, and has a long treatment time with no guarantee of success rate. All these factors have made cancer treatment a burden to the healthcare system. Besides, cancer treatment usually involves malign surgery, chemotherapy and radiation therapy can lead to numerous severe side effects that affect patients' quality of life.

Concerning this, populations are trying to find alternative ways to replace or complement modern medicine as adjuvant therapy for cancer. In recent years, numerous dietary phytochemicals, including polyphenols such as flavonoids and tannins, have been widely studied for their biological activities (Amar et al., 2017). In light of the continuing need for new effective anticancer agents, the phytonutrients from herbs and plants have received attention as the potential for alternative cancer treatment due to natural, lower cost and easy accessibility. Malaysia is rich in biodiversity and contains a wide variety of herbs and plants used in traditional medicine and general folklore medicine (Mainasara, Abu Bakar & Linatoc, 2018).

Cashew shoot is a well-known herb among the Malaysian community as they are

consumed as *ulam*. It is low cost, widely available and easily accessible among all Malaysian communities (Bachok et al., 2014). As more studies have been done on another part of cashew, further research about theanticancer properties of cashew shoot can provide more information on the potential of its medicinal properties. The finding data can provide insight for developing alternative functional food that can be incorporated into daily diet that benefits all Malaysia's community, especially cancer patients. Additionally, the finding data can contribute to new recommendations for cashew shoot inclusion, especially for populations with a high prevalence of cancer.

1.3 Significance of Study

Studies have proven that cancer is linked to numerous risk factors, and we are exposed to all these risk factors in numerous circumstances. Among them are stress, cigarettes, air pollution, alcohol intake, exposure to sunlight, physical inactivity and diet habits that lead to the free radical generation that causes oxidative stress when it exceeds the antioxidant capacity of the body system (Zima et al., 2001). Oxidative stress has been involved in numerous pathway that leads to inflammation. Inflammation is crucial to the development of cancer cells and promotes tumorigenesis of all stages (Gretten & Grivennikov, 2019).

While the prevalence of cancer is high among the population, the current treatment and therapeutic interventions involve chemotherapy, radiotherapy, and malign surgery with low therapeutic efficiency, high cost, and severe side effects that affect cancer patients' quality of life. Thus, more research on effective cancer treatments is needed that is free from side effects, low cost and easily accessible. One of the efforts involved is natural bioactive phytochemicals from plants and herbs that exhibit anticancer properties that can be introduced as a part of daily dietary intake (Trouillas et al., 2003). Besides, plants and herbs as part of the dietary therapy approach can increase public awareness about healthy diet habits especially involving recommended serving of vegetables and fruits to lower the risk of chronic disease, including cancer (Briguglio et al., 2020). Moreover, the introduction of herbs and plants as parts of the diet can contribute to daily fibre intake that has been shown to improve health status. This can be served as a prevention and treatment purpose to reduce nationwide cancer incidence.

In recent years, the adoption of Complementary and Alternative Medicine has been more frequently among cancer patients, especially for herbal ingredients. Complementary medicine has been defined by the World Health Organization (WHO) as a comprehensive set of healthcare practices that are not conventional and yet to be fully incorporated into most of the healthcare system. (Jermini et al., 2019). The adoption of complementary medicine is often deemed safe, natural or free of detrimental potentials by users (Tascilar et al., 2006). Other than that, it is capable of oral consumption, low cost, a known mechanism of action, and generally accepted by the public (Siddiqui et al., 2006). For example, green tea has been widely used due to its protective effect against prostate cancer (Jian et al., 2004). Phytoestrogen, which is abundant in soybeans and flaxseed, is associated with the capability to lower the risk of breast cancer (Yamamoto et al., 2003). Besides, several Chinese Herbal Medicine such as astralagus, turmeric,

ginseng is commonly used by cancer patients for cancer treatment and to reduce toxicity caused by chemo or radiotherapy. Several clinical studies have indicated the potential of suppressing tumour progression, improving the function of the immune system along with tissue damage induced by chemo and radiotherapy that provide helpful insight for future development of complementary medicine for cancer therapies (Yin et al., 2013).

Meanwhile, complementary medicine is commonly used among Malaysian cancer patients as well. For example, *Clinathanus nutans,* known as Sabah snake, *Areca catechu,* known as betel nut and *Piper betle,* known as betel leaf, were some of the most common herbs for cancer patients in Malaysia (Farooqui et al., 2016). It was described that the use of herbal products intends to slow down the specific cancer disease progression, improve body immunity, relieve symptoms and reduce the side effects caused by cancer treatments (Farooqui et al., 2016; Jermini et al., 2019). The commonuse of herbal ingredients by cancer patients may provide insight for researchers to evaluate the potential efficacy and safety of different herbs as complementary and alternative medicine for cancer patients (Farooqui et al., 2016).

1.4 Research Objectives

1.4.1 General Objective

To study the anti-proliferative effects of cashew shoots extract against breast, liver and colorectal cancer cells and phytochemicals screening of cashew shoots extract.

1.4.2 Specific Objectives

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

2. To determine cell cycle analysis of cashew shoots extract in human breast cancer cell line (MDA-MB-231), human liver cancer cell line (HepG2) and human colon cancer cell line (HT-29) cells using flow cytometry.

3. To determine phytochemical compounds in 70% ethanolic extract of cashew shoot using LCMS analysis.

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