UNIVERSITI PUTRA MALAYSIA

PHYTOCHEMICAL ANALYSIS AND CYTOTOXIC EFFECTS OF MANGO (Mangifera indica L) KERNEL ON BREAST CANCER CELL LINES

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By

AL-SHWYEH HUSSAH ABDULLAH

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Breast cancer is a significant cause of morbidity and mortality among women around the world. Currently, anticancer research focuses are on the discovery of alternative therapeutic compounds from natural products. Although numerous study has been done on plants to discover new drugs for the treatment of chronic diseases like cancer, the products of the mango plant species *Mangifera indica* L. waterlily, particularly the kernel have not adequately investigated. In this study the *M. indica* waterlily kernel ethanolic extract are investigated to determine its chemical components and anticancer effect. It is postulated that *M. indica* waterlily kernel extract has antibreast cancer activities through the antioxidant properties of its constituent compounds. Thus, the objective of this study is to determine and characterize the content of the ethanolic *M. indica* waterlily kernel extract and determine the antibreast cancer effect of the extract. The *M. indica* waterlily kernel extract was characterized by high performance liquid chromatography-mass spectrometry and gas chromatography-mass spectrometry and its antioxidant potentials determined by 2,2-diphenyl-1-picrylhydrazyl and ferric-reducing antioxidant power assays and determination of its thiobarbituric acid reactive substances and glutathione and reactive oxygen species contents. The cytotoxicity of the extract on breast cancer MDA-MB-231 and MCF-7 cells and normal breast MCF-10A cells was assessed by neutral red uptake, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, and lactate dehydrogenase release assays and morphological studies, using doxorubicin as the control. The effects of the extract on apoptosis-related markers (Bcl-2, Bax, p53 proteins and Caspase-3, -8 and -9) were also assessed to determine mechanism of cell death. The results showed that *M. indica* waterlily kernel extract has many bioactive compounds especially phenolics such as phenolic acid, flavonoides and xanthones. When chemical components of the extract was test against the breast cancer cell line, it was shown that mangiferin, rutin, chlorogenic acid and myricetin, but not p-coumaric acid or epigallo-catechin, exhibited significant cytotoxic effects against the breast cancer cell only, not the normal cells. It was therefore assumed that it is the mangiferin, rutin, chlorogenic acid and myricetin content of the *M. indica* kernel extract that contributed towards the cytotoxicity. The extract has high antioxidant potentials, and induced cytotoxicity in MDA-MB-231 and MCF-7 cells lines in a dose- and time-dependent manner, but was not toxic to the normal breast cells, MCF-10A. It is suggested that the anticancer effect of the *M. indica* extract is via modulation of redox status through its antioxidant constituents and

induction of apoptosis. These findings suggest that *M. indica* kernel extract, with antiproliferative properties towards cancer cells, while relatively innocuous to normal cells, is a good candidate as an alternative to or for supplementation for current chemotherapies in the treatment of breast cancers, without showing the side-effects associated with these anticancer drugs.

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

ANALISA FITOKIMIA DAN KESAN BIJI TERATAI MANGIFERA INDICA KE ATAS KANSER PAYUDARA

Oleh

AL-SHWYEH HUSSAH ABDULLAH

November 2015

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Kanser payudara merupakan penyebab kemorbidan dan kematian yang ketara dalam kalangan wanita di seluruh dunia. Kini, penyelidikan antikanser tertumpu kepada penemuan sebatian terapeutik alternatif daripada produk semula jadi. Walaupun banyak kajian telah dijalankan untuk menemuikan drug baharu untuk rawatan penyakit kronik seperti kanser, produk daripada spesies pokok manga, *Mangifera indica* L., terutama isirongnya belum banyak diselidik. Dalam kajian ini, ekstrak etanol isirong mangga *M. indica* diselidik untuk menentukan komponen kimia dan kesan antikansernya. Adalah dipostulat bahawa ekstrak isirong mangga *M. indica* mempunyai aktiviti antikanser payudara melalui sifat antioksidan sebatian yang terkandung di dalamnya. Justeru, objektif kajian ini ialah untuk menentu dan mencirikan kandungan ekstrak etanol mangga *M. indica* dan menentukan kesan antikanser payudara ekstrak ini. Estrak mangga *M. indica* dicirikan mengguna kromatografi prestasi tinggi-spektrometri jisim dan kromatografi gas-spektrometri jisim dan potensi antioksidannya ditentukan melalui assai 2,2-difenil-1-pikrilhidrazil dan kuasa antioksidan penurunan ferik, dan melalui penentuan kandungan bahan reaktif asid tiobarbiturik and spesies oksigen reaktifnya. Kesan antikanser *in vitro* 5, 10, dan 50 µg/mL ekstrak terhadap titisan sel kanser payudara MDA-MB-231 dan MCF-7 dinilai melalui assai pengambilan merah neutral, 3-(4,5-dimethiltiazol-2-yl)-2,5-difeniltetrazolium bromide, pembebasan laktat dehydrogenase, dan kajian sitologi. Kawalan positif diguna dalam kajian ini ialah doksorubisin. Mekanisme kematian sel telah ditentukan melalui assai protein Bcl-2, Bax, and p53 and kaspase-3, -8 dan -9. Kematian sel ini telah disahkan melalui perubahan apoptosis pada morfologi sel terperlaku. Hasil kajian menunjukkan bahawa ekstrak mangga *M. indica* mempunya banyak sebatian bioaktif khususnya fenolik seperti asik fenolik, flavonoid dan xanton. Pengesanan sebatian ini paling sensitif jika kaedah hidrolisis diguna dalam penyediaan ekstrak. Apabila komponen kimia extrak diuji terhadap titisan sel kanser payudara, di dapati mangiferin, rutin, asid klorogenik dan mirisetin, bukan asid p-koumarik atau epialo-katekin yang menunjukkan kesan sitotoksik tererti terhadap sel kanser payudara sahaja, bukan terhadap sel normal. Justeru, adalah diandaikan yang mangiferin, rutin, asid klorogenik dan mirisetin dalam ektrak isirong mangga *M. indica* yang menyumbang kepada kesitoksikan. Ekstrak ini mempunyai potensi antioksidan yang tinggi, dan mengaruh kesitotoksikan titisan sel MDA-MB-231 dan MCF-7 secara bersandarkan dos dan masa, tetapi tidak toksik terhadap sel normal, MCF-10A. Adalah disarankan yang kesan antikanser ekstrak

mangga *M. indica* adalah dengan mengurangkan tekanan oksidatif melalui kandungan antioksidannya dan mengaruh apoptosis. Penemuan ini menyarankan ekstrak mangga *M. indica* dengan sifat antipemproliferatannya terhadap sel kanser, sambil tidak memudaratkan sel normal, adalah calon baik sebagai bahan alternatif dan penambah untuk kemoterapi kini diguna dalam rawatan kanser payudara, tanpa menunjukkan kesan sampingan yang terkait dengan drug antikanser tersebut.

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ATP	adenosine triphosphate
Afap-1	actin Filament Associated Protein 1
Bak	Bcl-2 antagonistic killer
Bax	Bcl-2-like protein 4
Bcl-xL	B-cell lymphoma-extra large
BHT	Butylatedhydroxytoluene
Bid	BH3 interacting-domain death agonist
BRCA1	breast cancer 1-early onset
BRCA2	breast cancer 2-early onset
c-FLIP	Cellular FLICE (FADD-like IL-1β-converting enzyme)-inhibitory protein
DAD	diode array detector
DMEM	Dulbecco's modified Eagle medium
DMSO	Dimethylsulphoxide
DNA	Deoxyribonucleic acid
DPPH	2,2-diphenyl-1-picrylhydrazyl
DRI	dietary reference intake
E2	17-β estradiol
EGC	epigallocatechin
EGCG	Epigallocatechin gallate
ER-	Estrogen receptor negative
ER+	Estrogen receptor positive
ESI-MS	Electrospray ionization mass spectrometric
FADD	Fas-Associated protein with Death Domain

FAS	Fas ligand
FIC	Ferrous ion chelatingFBS: Fetal bovine serum
FRAP	Ferric reducing acid potential
FSH	follicle stimulating hormone
GCMS	Gas chromatography–mass spectrometry
GSH	Glutathione
HER2	human epidermal growth factor receptor 2
HPLC	High performance liquid chromatography
IAPs	inhibitors of apoptosis
IHC	Immunohistochemistry
LCMS	Liquid chromatography–mass spectrometry
LDH	Lactate dehydrogenase
M. indica	*Mangifera indica*
MDA	Malondialdehyde
MTT	Thiazoyl blue tetrazolium bromide
MW	molecular weight
NADH	Nicotinamide adenine dinucleotide
NR	Neutral red
p53	p53 tumor suppressor
PBS	Phosphate buffer saline
PR	Progesterone receptor
RNA	Ribonucleic acid
ROS	Reactive oxygen species
RT	retention time
TEP	total extractable polyphenols
TBARS	Thiobarbituric acid reactive species

TNF	tumor necrosis factor
TPC	Total phenolic content
TRAIL	TNF-related apoptosis-inducing ligand
WHO	World Health Organization

CHAPTER 1

INTRODUCTION

Breast cancer is the most common cancer among women and causes the highest mortality among cancers. In the past, breast cancer burden was most prevalent in the developed countries but in recent years, the incidence in developing countries is also rising. Over 1 million people have been diagnosed with breast cancer while over 400,000 die from the disease every year [Coughlin & Ekwueme, 2009; Ferlay *et al*., 2004; Jemal *et al*., 2011]. Although there are many factors involved in the pathogenesis and progression of breast cancer, oxidative stress is thought to play a significant role [Hakkak *et al*., 2013; Reuter *et al*., 2010]. Estrogen treatment is implicated in the causation of increased oxidative stress in breast cancer [Sastre-Serra *et al*., 2010].

There are many treatment modalities for breast cancer including surgery, chemotherapy and radiation that pose very heavy financial burdens on patients and health authorities [Radice & Redaelli, 2003]. Multidisciplinary approach is recommended for treatment of breast cancers, although there are serious side-effects associated with these treatment options [Saini *et al*., 2011]. Recent studies have indicated that the use of plant bioresources for the management of breast cancer may offer relatively safer alternatives in comparison with currently available chemotherapy agents. Additionally, the considerations of the high financial burden related to chemotherapy agents is driving the search for cheaper alternatives [Mukherjee *et al*., 2001]. The need for alternatives is further underscored by the fact that chemotherapy agents can cause serious and debilitating long term health effects. Already, fruits and vegetable consumption has been linked with reduced risks of chronic diseases including cancers [Willett, 2010]. The effect of these diets is mostly attributable to their antioxidants properties [Borek, 2004]. These observations are driving the search for newer alternative therapies for cancers that are safer and more cost-effective.

Mango (*Mangifera indica* L.), a member of the family *Anacardiaceae*. *M. indica*, has become naturalized and adapted to the environment of the subtropics and tropics [Rocha Ribeiro *et al*., 2007]. There are over 500 classified *M. indica* varieties throughout the world. The genus of *Mangifera* consists of 69 species and mostly restricted to tropical Asia [Ramanatha Rao & Mal 2002; Yonemori *et al*., 2002]. Malaysia is a tropical country with heavy precipitation, high temperatures, and high humidity that favors *M. indica* vegetation. Malaysia, particularly the peninsular area, has variety of mangoes; the better known cultivars are Golek (MA 162), Masmuda (MA 204), Maha 65 (MA 165) and Chok Anan (MA 224) [Yonemori *et al*., 2002]. Generally, Chok Anan is very suitable for the export market as it has desirable color and sweetness and good flavor. Mangoes are rich in vitamins, minerals, anti-oxidants and other bioactive compounds [Ribeiro *et al.*, 2008; Soong & Barlow, 2004; Soong & Barlow, 2006] and these are heavily consumed causing accumulation of waste. Similarly, *M. indica* seed kernels are usually wasted during processing although recent studies have indicated that they contain useful bioactive compounds that may potentially confer functional effect [Fowomola, 2010; Nkizou *et al*., 2010]. Thus, with appropriate treatment, and understanding of the chemical and functional characteristics of the kernel, the mango waste can be used as a food ingredient and in nutraceutical or pharmaceutical applications. It is in view of the current drive to find cheaper and safer alternatives to chemotherapy agents and the rich bioactive composition of *M. indica* seed kernel that the present study was conceived to study the potential anti-breast

cancer effects of *M. indica* kernel extract. Moreover, *M. indica* is reported to be antioxidant-rich, and foods with potent antioxidant potentials have been shown to regulate cancer cell growth via modulating the redox status of the cells and inducing apoptosis [Ghasemzadeh & Ghasemzadeh, 2011]. Thus, the phytochemical composition and antioxidant potentials of *M. indica* kernel extract, and its potential anticancer effects were evaluated *in vitro* on breast cancer cell lines.

The study aims to evaluate the cytotoxic effect of the extract from the kernel of *M. indica* towards breast cancer cell lines to determine its utility as complementary or alternative anti-breast cancer compound.

Study Hypothesis:

It is hypothesized that the solvent extract of *M. indica* kernel

1. contains anti-oxidative compounds.
2. has cytotoxic effects towards breast cancer cell lines.
3. has minimal cytotoxicity towards normal breast cell lines.

General objective:

The main objective of the study is to determine the composition of bioactive compounds in *M. indica* kernels and their anti-breast cancer cell properties.

Specific objectives:

The specific objectives are to;

1. obtain a solvent extract of *M. indica* kernel and determine its compositional analysis.

2. determine the antioxidant properties of *M. indica* solvent extract.

3. determine the *in vitro* cytotoxicity effect of *M. indica* solvent extract on MCF-7 and MDA-MB-231 breast cancer cell lines.

4. determine the anticancer mechanism of *M. indica* solvent extract.

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