SCURRULA FERRUGINEA METHANOL EXTRACT INDUCES REACTIVE OXYGEN SPECIES-MEDIATED AND MITOCHONDRIAL-DEPENDENT APOPTOSIS IN BREAST CANCER CELLS

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I would like to dedicate this thesis to my beloved wife, my lovely unborn child and my lovely father and mother
for their endless support and encouragement

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ABSTRACT

The purpose of this study is to investigate antioxidant and anticancer activities of *Scurrula ferruginea* extracts. The antioxidant activities of the extracts were evaluated using various assays. The extracts were further investigated to examine their cytotoxic activity on human breast cancer cell lines; MDA-MB-231, MDA-MB-468 and MCF-7 using MTT assay. Microscopic examinations of cells were carried out to elucidate the modes of cell death. The effect of the extracts on cancer cells colony formation and migration were determined. Changes in mitochondrial membrane potential and level of reactive oxygen species (ROS) were measured. Western blot and cell cycle analysis were performed to unravel the mechanism of action of extracts against the breast cancer cells. Using GC-MS analysis, chemical composition of extracts were characterized to reveal the presence of anti-cancerous compounds. Our study on stem methanol extract has shown the highest amount of phenolic, flavonoid contents, strong DPPH radical scavenging and metal chelation activity in comparison to other extracts. The stem aqueous and methanol extracts have shown higher cytotoxic effect towards MDA-MB-231 cells compared to other cell lines with IC_{50} value of 50.35 and 19.27 µg/mL, after 72 h of treatment, respectively. Morphological observations revealed properties of apoptosis in the treated cells. The results displayed that the extracts have the ability to stop migration of cancer cells and also inhibit the colony formation of cancer cells. Moreover, the results have shown that the extracts induced apoptosis in breast cancer cells by ROS generation and mitochondrial depolarization. Furthermore, this study demonstrated that methanol extract inhibited the proliferation of breast cancer cells via induction of cell cycle arrest at G0/G1 phase and apoptosis through a mitochondria-dependent apoptosis pathway. The findings of present study revealed the potential antioxidant and anticancer activities of *S. ferruginea* stem methanol extract which may serve as a promising candidate in the search of a new anti-cancer drug.

ABSTRAK

Tujuan kajian penyelidikan ini adalah untuk mengkaji aktiviti antioksida dan antikanser bagi ekstrak *Scurrula ferruginea*. Aktiviti antioksida bagi ekstrak dianalisa menggunakan pelbagai kaedah asai. Ekstrak tersebut juga dikaji secara lebih mendalam untuk mengenal pasti aktiviti sitotoksik terhadap garisan sel kanser payudara; MDA-MB-231, MDA-MB-468 dan MCF-7 menggunakan asai MTT. Analisis mikroskopik terhadap sel-sel telah dilaksanakan untuk menghuraikan mod kematian sel. Kesan daripada ekstrak terhadap pembentukan dan migrasi koloni kanser telah ditentukan. Perubahan kepada keupayaan membran mitokondria dan tahap reaktif spesies oksigen (ROS) telah diukur. Western blot dan analisis kitaran sel telah digunapakai untuk menguraikan mekanisme tindakan bagi ekstrak terhadap sel-sel kanser payudara. Dengan menggunakan analisis GC-MS, komposisi kimia bagi ekstrak telah dicirikan dan menunjukkan kehadiran sebatian anti-kanser. Ekstrak methanol batang memberikan kuantiti fenolik dan flavonoid yang sangat tinggi serta aktiviti penyingkiran radikal DPPH dan pengelatan logam yang kukuh berbanding ekstrak yang lain. Ekstrak akueus dan methanol dari batang menunjukkan kesan sitotoksik yang lebih tinggi terhadap sel MDA-MB-231 berbanding garisan sel yang lain dengan nilai IC_{50} masing-masing sebanyak 50.35 dan 19.27 µg/mL setelah 72 jam rawatan. Pemerhatian morfologi mendedahkan ciri-ciri apoptosis dalam sel-sel yang dirawat. Hasil kajian menunjukkan bahawa ekstrak-ekstrak tersebut mempunyai keupayaan untuk memberhentikan migrasi sel-sel kanser di samping menghalang pembentukan koloni sel-sel kanser. Tambahan pula, hasil kajian menunjukkan bahawa ekstrak-ekstrak mencetuskan apoptosis dalam sel-sel kanser payu dara melalui penjanaan ROS dan penyahkutuban mitokondria. Selain itu, kajian ini juga menunjukkan bahawa ekstrak methanol menghalang penyebaran sel-sel kanser payu dara dengan merencatkan kitaran sel pada fasa G0/G1 dan apoptosis melalui satu laluan apoptosis yang mempunyai pergantungan terhadap mitokondria. Hasil kajian menunjukkan bahawa aktiviti antioksida dan antikanser bagi ekstrak methanol dari batang *S. ferruginea* berpotensi menjadi calon kepada pencarian ubat anti-kanser baru.

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NCR	-	The National Cancer Registry
DCIS	-	Ductal Carcinoma In Situ
LCIS	-	Lobular Carcinoma In Situ
HER	-	Human Epidermal Growth Factor Receptor
ER	-	Estrogen Receptor
PR	-	progesterone receptor
NCI	-	National Cancer Institute
ROS	-	Reactive Oxygen Species
CAM	-	Complementary and Alternative Medicine
DPPH	-	Diphenyl-2-picryl hydrazine
ABTS	-	2, 2'-azino bis-(3-ethyl benzo thiazoline-6-sulphonic acid)
EDTA	-	Ethylenediaminetetraacetic acid
DMEM	-	Dulbecco’s Modified Eagle Medium
FBS	-	Fetal Bovine Serum
PI	-	Propidium Iodide
PBS	-	phosphate buffer saline
DMSO	-	Dimethyl Sulfoxide
TPC	-	Total Phenolic Content
TFC	-	Total Flavonoid Content
GC-MS	-	Gas chromatography-mass spectroscopy
RPMI	-	Roswell Park Memorial Institute

PDT	-	Population Doubling Time
MTT	-	Thiazolyl Blue Tetrazolium Bromide
AO/EB	-	Acridine orange/Ethidium bromide
MMP	-	Mitochondrial Membrane Potential
BCA	-	Bicinchoninic Acid
BSA	-	Bovine Serum Albumin
SDS-PAGE	-	Sodium dodecyl sulfate polyacrylamide gel electrophoresis
AP	-	Alkaline Phosphatase
MOMP	-	Mitochondrial Outer Membrane Permeabilization
DISK	-	Death-Inducing Signaling Complex
ML-I	-	Mistletoe Lectin I
HR-QOL	-	Health-Related Quality Of Life
VA	-	*Viscum album*
ADCC	-	Antibody-Dependent Cell-mediated Cytotoxicity
TNFα	-	Tumor Necrosis Factor alfa
CRF	-	Cancer Related Fatigue
TCM	-	Traditional Chinese Medicine
LS	-	Life Satisfaction
TEAC	-	Trolox Equivalent Antioxidant Capacity
RT	-	Retention Time

CHAPTER 1

INTRODUCTION

1.1 Research Background

1.1.1 Breast Cancer

Cancer of breast formed due to formation of malignant tumor in the cells of breast. Initially the growth of breast cancer is local which is followed by extension within lymph vessels into regional lymph nodes and invasion of small vein which results in systematic metastatic spread (Spratt & Tobin, 1995). Breast cancer is the most common type of non-skin malignancy among women worldwide. It has been reported that the incidence and mortality of breast cancer have increased during the last two decades (*American Cancer Society Global Cancer Facts & Figures 2nd Edition,* 2011; Jemal *et al*., 2011; Ferlay *et al*., 2013). Based on 2006-2010 statistics, the number of deaths in the United States was 22.6 per 100,000 women per year. It is predicted that an estimated 231,840 new cases of breast cancer and 40,730 breast cancer-related deaths will occur among women in 2015 worldwide ("American Cancer Society. Cancer Facts & Figures," 2015)

The incidence rate of breast cancer is highest in North America with the age standardized rates of 99.4 per 100,000 population, followed by countries in the Eastern Europe, South America, Southern Africa, and western Asia with moderate incidence rates, while the lowest incidence rates are reported in most African countries (Yip *et al*., 2006; Ferlay *et al*., 2010).

It is reported that approximately one million female are diagnosed with breast malignancy with an estimated 410,000 deaths every year, worldwide (Coughlin & Ekwueme, 2009). The incidence and mortality of breast cancer was reported lower in low-resource countries compared to high-resource countries (Smith, 2006). In most of the Asian countries, the incidence rate of breast cancer is increasing *(*Abdullah *et al*., 2013). An increasing in the prevalence of breast cancer was reported in Malaysia as well (Abdullah *et al*., 2013). The highest incidence rate for breast cancer in Malaysia was observed at women between 50-60 years old (Dahlui *et al*., 2011). It is estimated that one out of twenty Malaysian women have chance to get breast cancer at some point of their lives (Dahlui *et al.*, 2011).

Breast cancer is the most common cancer among Malaysian women (Lim *et al*., 2008). The National Cancer Registry (NCR) 2003-2005 reported an age-standardized rate (ASR) of 47.3 per 100 000. The incidence is highest in Chinese (59.9 per 100 000) followed by Indians (54.2 per 100 000) and Malays (34.9 per 100 000) (Lim *et al*., 2008). The International Agency for Research in Cancer (GLOBOCAN) 2012 estimated the ASR of breast cancer in Malaysia as 38.7 per 100,000 with 5410 new cases in 2012 (“http://globocan.iarc.fr,”).

1.1.2 Breast Cancer Treatment

Different treatment options are currently available including local therapy and systemic therapy. Local therapy includes surgery, radiotherapy or a combination of the two, applied to kill cancer cells from a limited (local) area such as lymph nodes, breast and chest wall. Systemic therapy includes endocrine or hormone therapy and chemotherapy which administered following primary surgery or radiotherapy to kill or inhibit metastases and to improve survival. Table 1.1 represents various methods of breast cancer treatment and their common side effects. Selection of treatment strategies depend on tumor size, metastatic potential, axillary lymph node status and molecular and patient profile (Liao *et al*., 2013). Systemic therapy with cytotoxic chemotherapy and endocrine therapy were found to be effective in prolonging disease-free and survival time (Peto *et al.*, 2000).

Table 1.1: Summary of various methods of breast cancer treatment and their common side effects.

Methods	Mechanism of action	Side effects	References
Surgery	Conservative and mastectomy	Lymphedema, chronic nerve damage, infection at the incision site, armpit discomfort	(Karen *et al*., 2002; Ridner *et al*., 2011)
Radiotherapy	Using high dose of radiation	Skin reactions of the area being radiated	(Sjövall *et al*., 2010)
Biological targeted therapy	Using monoclonal antibody and medicine Herceptin (Trastuzumab) Tykerb (lapatinib)	 Weakness, diarrhea, Pain, fever Itchy and dry skin, diarrhea	(Nahta *et al*., 2006)
Endocrine or hormone therapy	Using aromatase inhibitors and tamoxifen by blocking the action of estrogen Tamoxifen: Aromatase inhibitors:	 Vaginal discharge, an increase in thromboembolic events and uterine sarcoma Musculoskeletal adverse effect ,hot flashes, increased LDL, loss of libido, vaginal dryness	(Kalidas & Brown, 2005; Connor & Attai, 2013)
Chemotherapy	The most commonly type of treatment using anti-breast cancer drugs Carboplatin, Cisplatin: Cyclophosphamide:	 Nephrotoxicity Pulmonary toxicity	(Yao *et al*., 2007; Chandwani *et al*., 2012; Gianni *et al*., 2008)

Despite of varied side effects, using chemotherapy either as a single compound or combination therapy with multiple-agents is still the most commonly used treatment option by breast cancer patients (Ozer *et al*., 2000). Chemotherapy uses anti-breast cancer drugs and cytotoxic agents for treatment of metastatic breast cancer (ER-negative tumors). Tumor cell response to chemotherapy and cytotoxic agents through an active form of cell death is known as apoptosis or programmed cell death. It is now well stablished that other modes of cell death such as necrosis and autophagy also take place following chemotherapy in tumor cells (Brown & Attardi, 2005).

1.2 Problem Statement

Although many treatment methods are currently established including surgery, radiotherapy, biological therapy, hormone therapy and chemotherapy, these therapies are less effective and recurrence is still occurring in breast cancer patients due to side effects and toxicity of drugs in normal cell and aggressive behaviour of the tumours (Table 1.3). In spite of many improvement in the use of hormonal and adjuvant cytotoxic therapies in breast cancer patients, there is no considerable reduction in mortality of breast cancer today (Eggenschwiler *et al*., 2007). Costly treatment methods and serious side effects associated with available therapies may cause greater tendencies among people to use herbal medicines for health care.

Complementary and alternative medicine (CAM) as one of the major aspect of cancer therapy has been developed in last few years in order to alleviate drug side effects and relief pain in breast cancer patients (Ostermann *et al*., 2009). A large proportion of cancer patients (up to 80%) use complementary and alternative medicine (CAM) (Vardy *et al*., 2013). Breast cancer patients are among the most likely users of CAM (Bennett *et al*., 2009). Among CAM, herbal supplements (anti-oxidants) is the most commonly used group of cancer treatment. Cancer treatment using herbal medicine has a history of more than 2000 years (Craig, 1999).

Harmful effects of conventional treatment as well as toxicity of chemotherapy create a significant problem in breast cancer therapy. The alternate solution to decrease side effects of chemotherapeutic drugs is the use of medicinal plants. Use of medicinal plants which have fewer side effects as compared to synthetic drugs can provides an alternative to the use of conventional allopathic medicine for treatment of breast cancer. In addition, any practical solution to manage cancer progression is of paramount importance. Therefore, there is a need to evaluate whether medicinal plant extracts are able to act as potent anticancer agent by controlling the cancer progression or arresting the carcinogenic process.

Previous research findings have shown that various European mistletoe extracts from different host trees are capable of inducing apoptosis and cell death in numerous tumor cells and human cancer cell lines (Ramaekers *et al*., 2007; Harmsma *et al*., 2006).

Although various studies investigated the effect of European mistletoe on cancer, not many studies focused on other species of mistletoe from other continents. Malaysia's rainforest being part of the world's tropical rainforest is also considered as one of the most evolved and diverse rainforest in the world. *Scurrula. ferruginea* is one of the mistletoe species in Malaysia which is used as a folk medicine for treatment of several ailments (Barlow, 1991). It has been reported that a decoction of *S. ferruginea* leaves along with *Millettia sericea* used for bathing malarial patients. In addition, a poultice of the pounded leaves administered as a post-partum protective medicine and also applied for snake bite and wound (Burkill *et al*., 1966) (Perry, 1978). Moreover, this plant are traditionally employed in the treatment of many diseases including gastrointestinal malfunction, high blood pressure and hypertension (Ameer *et al*., 2009).

Ethno-medical knowledge plays an important role in selection of plants for discovery of novel drugs. Therefore, *S. ferruginea* was selected for the present study based on its reputation in folk medicine. There is no report on antioxidant capacity, anticancer activity and mechanism of action of *S. ferruginea*. The current study

provide the scientific rational for antioxidant and anti-breast cancer activities of *S. ferruginea.*

1.3 Objectives of Study

Based on the above-mentioned problem statements, the objectives of the present study are as follow:

1. To evaluate potential of *S. ferruginea* crude extracts based on the antioxidant activity and phytochemical analysis
2. To investigate the selective cytotoxic effects of selected extracts on breast cancer cells and study apoptosis-inducing effects of extracts
3. To study the mechanism of growth arrest and unravel apoptotic pathway involve in breast cancer cell death by selected extract

1.4 Scope of Study

Aerial parts of *S. ferruginea* (Jack) Danser including stems, leaves and flowers were used in the present study. Different types of breast cancer cell lines including MCF-7 (luminal A breast carcinoma), MDA-MB-231(Claudin-low breast carcinoma) and MDA-MB-468 (basal-like breast carcinoma) which are differ in molecular markers status and invasiveness have been selected for the present study.

To achieve the listed objectives, the study was confined to the following scopes:

1. Determination of total phenolic and total flavonoid content by Folin-Ciocalteu and aluminum chloride methods, respectively and antioxidant activities of different extracts by assessing DPPH free

radical scavenging activity, ABTS and metal chelation capacity of *S. ferruginea* extracts.

2. Analysis of chemical composition using GC-MS of *S. ferruginea* extracts.

3. Evaluation of selective cytotoxic activities of selected extracts against breast cancer cell lines and non-cancerous cell line using MTT assay and characterization of the cell death using AO/EB and Hoechst/PI staining methods.

4. Determination of cell migration inhibition efficiency and colony forming ability of treated cancer cells using scratch assay and colony forming assay respectively.

5. Measurement of mitochondrial membrane potential by JC-1 assay and investigation on the potential mechanism of apoptosis as the result of oxidative stress by measuring intracellular ROS level using DCF-DA assay.

6. Determination of cell death mechanism pathway of selected extract against breast cancer cell through the regulation of bcl-2, bax, caspase-3, caspase-7 and PARP proteins using western blot analysis and possible cell cycle arrest using flow cytometric analysis.

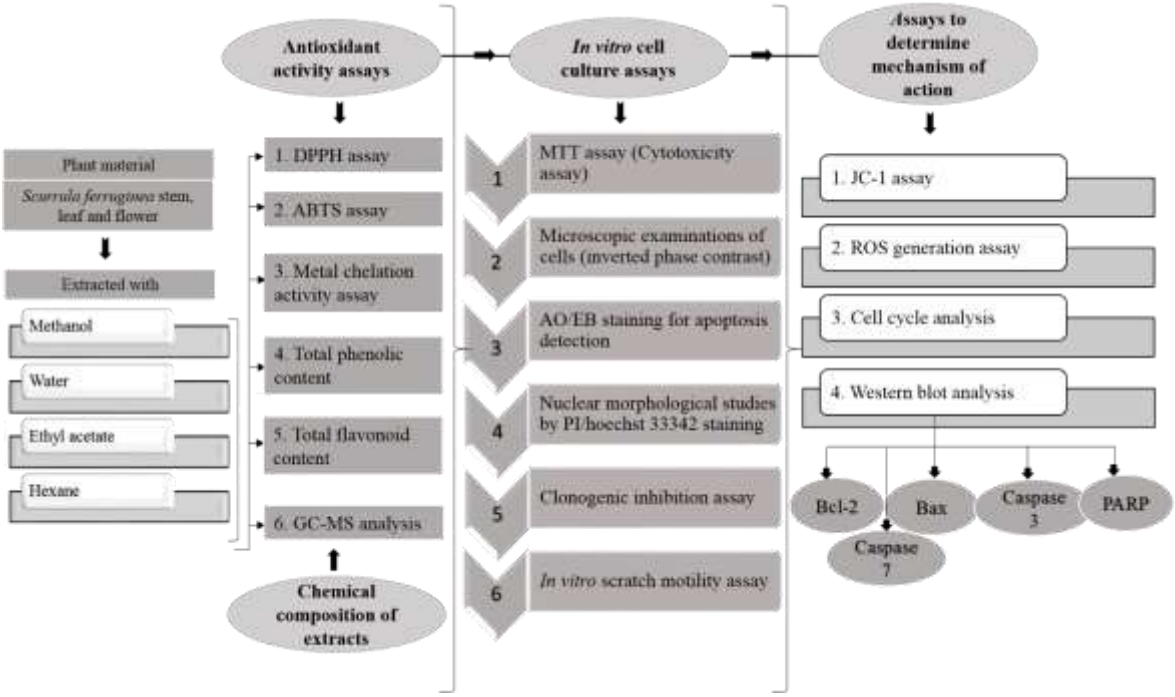
1.5 Significant of Study

i. Growth inhibitory effects on different carcinoma cell types may be crucial for effective control of breast cancer; therefore, the present study is of great importance to introduce a novel candidate in battling breast cancer particularly ER-negative breast carcinoma.

ii. The present study is also paving the way for further research on *S. ferruginea* in the field of pharmaceutical industry and anti-cancer drug discovery for the development of anticancer agents.

iii. This study provides an experimental basis for systematic and clinical research of medicines for treatment of breast cancer in the future.

1.6 Methodology



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