
**UNIVERSITI PUTRA MALAYSIA**

# *CYTOTOXIC, ANTI-PROLIFERATIVE AND APOPTOTIC EFFECTS OF ZERUMBONE ON HUMAN AND MOUSE LEUKEMIC CELL LINES*

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By

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Zerumbone (ZER), is a sesquiterpene isolated from the edible plant *Zingiber zerumbet* Smith or locally known as lempoyang. It is used in local traditional medicine as a cure for swelling, sores and loss of appetite. In this study, the cytotoxic effect of ZER was tested against different types of cell lines including leukemia cells such as WEHI-3B (mouse myelomonocytic leukemia), HL-60 (human promyelocytic leukemia), CEM-SS (human T-lymphoblastic leukemia) and K-562 (human chronic myelogenous leukemia/ erythroleukemia), using the standard MTT assay. Results obtained showed that ZER was a potent cytotoxic agent to all leukemic cell lines tested with $CD_{50}$ below 10 µg/ml after 72 hours of exposure. The morphological observation of the cell lines tested using light microscope, revealed the apoptosis feature of the treated cells such as membrane blebbing, cell shrinkage, and formation of apoptotic bodies. WEHI-3B cells were then chosen as a model in the study of cell death mechanism as the cells were also used to induce leukemia in the *in vivo* study. The mode of cell death determined using acridine orange/propidium iodide (AOPI) staining and Annexin V-FITC flow cytometry technique further confirmed the

apoptotic effect of ZER with nuclear condensation and other apoptotic features clearly seen and the increased percentage of apoptotic cells ($p<0.001$) as compared to control and Doxorubicin (DOX) treated cells. The effect of ZER on the proliferation of leukemia cells was determined using MTT assay and the effect on cell cycle was identified using flow cytometry propidium iodide (PI) staining technique. Results showed that cell proliferation was inhibited at 48 hour of exposure and the cell cycle was arrested at $G_1$/S phase followed by apoptosis. The increased percentage of hipodiploid cells in the sub-$G_1$ phase of the cell cycle ($p< 0.001$) compared to control also indicated the involvement of apoptosis. The biochemical confirmation of cell death was done by analyzing the ZER treated DNA in agarose gel electrophoresis, whereas the involvement of executioner caspase-3 was also determined. The formation of DNA ladder confirmed the mode of cell death was through apoptosis mechanism and this was paralleled with caspase-3 activation found in ZER treated cells. The detection of gene expression involved in cell death was done using the MPCR (multiplex polymerase chain reaction) method, in which the expression of Bcl-2 and Bax genes in ZER treated cells further supported the apoptosis mechanism involved in ZER action. Furthermore, in order to evaluate the effectiveness of ZER in combating leukemia, the leukemic-induced mice were then treated with 10 mg/kg and 20 mg/kg body weight of ZER. The *in vivo* results showed that ZER has the capability of preventing the adverse effect of leukemic cells on the treated mice such as damaged to vital organs and able to maintain the white blood cells status compared to the untreated leukemic mice. Therefore, it can be concluded that ZER exhibited its antileukemic effect through apoptosis induction, capable of preventing the spreading of leukemia cells in leukemic-induced mice, and safe to be used as an antileukemia agent as it does not affect the blood profile or damaged to the vital organs.

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

**KESAN SITOTOKSIK, ANTI-PROLIFERATIF DAN APOPTOSIS ZERUMBONE TERHADAP SEL SELANJAR LEUKEMIA MANUSIA DAN MENCIT**

Oleh

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Zerumbone (ZER) merupakan seskuiterpen yang diasingkan daripada pokok *Zingiber zerumbet* Smith yang juga dikenali sebagai lempoyang. Dalam perubatan tradisional, ia digunakan untuk merawat bengkak, luka dan hilang selera makan. Kesan sitotoksik ZER dalam kajian ini ditentukan dengan kaedah piawai asai MTT terhadap beberapa jenis sel selanjar berbeza termasuk sel selanjar leukemia seperti WEHI-3B (mielomonositik mencit), HL-60 (promielositik manusia), CEM-SS (T-limfoblastik manusia) dan K-562 (mielogenus kronik/ eritroleukemia). Hasil kajian mendapati bahawa ZER adalah agen sitotoksik yang poten terhadap semua sel selanjar leukemia yang dikaji dengan nilai $CD_{50}$ di bawah 10 µg/ml selepas 72 jam waktu pendedahan. Perubahan morfologi sel diperhatikan dengan mikroskop cahaya dan didapati terdapat ciri apoptosis pada sel yang dirawat seperti bleb membran, pengecutan sel serta pembentukan jasad apoptosis. Sel WEHI-3B seterusnya digunakan sebagai model bagi mengkaji cara kematian sel kerana sel ini digunakan bagi mengaruh leukemia dalam kajian *in vivo*. Pewarnaan akridin jingga/propidium iodida (AOPI) mengesahkan kesan apoptosis ZER di mana kondensasi nukleus serta ciri lain

apoptosis jelas kelihatan. Peratus sel apoptotik juga lebih tinggi ($p<0.001$) berbanding sel kawalan dan yang dirawat dengan Doxorubicin (DOX). Hasil daripada kaedah Annexin V-FITC juga menunjukkan peningkatan peratus sel apoptotik ($p<0.001$) berbanding kawalan dan DOX. Kajian antiproliferasi ZER menunjukkan bahawa proliferasi sel direncat pada 48 jam waktu pendedahan manakala kesannya pada kitar sel yang ditentukan secara pewarnaan propidium iodida (PI) aliran sitometer, mendapati kitar sel diberhentikan pada fasa transisi $G_1$/S, diikuti dengan apoptosis. Peningkatan peratus sel hipodiploid dalam fasa sub-$G_1$ kitar sel ($p<0.001$) berbanding kawalan menunjukkan penglibatan apoptosis. Pengesahan biokimia kematian sel dilakukan dengan memisahkan DNA yang dirawat, secara elektroforesis gel agarosa, manakala penglibatan caspase-3 dalam kematian sel juga dikaji. Pembentukan *tetangga* DNA mengesahkan bahawa kematian sel adalah secara apoptosis dan ini selaras dengan pengaktifan caspase-3 pada sel yang dirawat dengan ZER. Seterusnya pengekspresan gen yang terlibat dalam kematian sel ditentukan menggunakan kaedah MPCR (*multiplex polymerase chain reaction*) dan didapati terdapat pengekspresan gen Bcl-2 dan Bax yang dikaitkan dengan apoptosis. Bagi menilai keberkesanan ZER dalam menentang leukemia, mencit yang diaruh leukemia dirawat dengan 10 mg/kg dan 20 mg/kg ZER. Perubahan fizikal mencit, histologi organ penting dan juga status sel darah putih diperhatikan dan dikaji. Keputusan kajian menunjukkan ZER berupaya menghalang kesan buruk sel leukemia pada mencit teraruh leukemia seperti kerosakan pada organ penting dan mengekalkan status sel darah putih berbanding tikus yang tidak dirawat. Oleh itu, boleh disimpulkan bahawa ZER menunjukkan kesan anti-leukemianya melalui aruhan apoptosis, menghalang penyebaran leukemia sel dalam mencit dan selamat digunakan kerana ia tidak mempengaruhi profil darah atau menyebabkan kerosakan pada organ penting.

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I certify that a Thesis Examination Committee has met on 10 May 2010 to conduct the final examination of Asmah binti Hamid on her thesis entitled "Cytotoxic, Anti-Proliferative and Apoptotic Effects of Zerumbone on Human and Mouse Leukemic Cell Lines" in accordance with the Universities and University College Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The committee recommends that the student be awarded the Doctor of Philosophy.

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

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## DECLARATION

I declare that the thesis is my original work except for quotations and citations which have been dully acknowledged. I also declare that it has not been previously, and is not concurrently, submitted for any other degree at Universiti Putra Malaysia or at any other institution

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**ASMAH BINTI HAMID**

Date: 10 May 2010

# CHAPTER I

# INTRODUCTION

## 1.1 Natural Products

Natural products have been a rich source of agents of medicinal values to modern medicine. Research on natural product potential as an alternative drug to treat various types of diseases is very much focused by researchers all over the world. Since many of the drugs used at present are reported to have side effects, the search for new kind of drugs from natural sources is intensifying. Among the sources are plant, animal, spongy, bacteria, fungi, virus, lichen and many others. Plants are the most natural product being studied so far, because it has been used as medicinal agents thousands of years ago. Normally, the active compounds extracted will be tested for their activity on cell culture (*in vitro*) and experimental animal (*in-vivo*) before they can be tested on human being.

The study of natural products is the investigation of their structure, formation, use and purpose in organisms. Drugs derived from natural products are usually secondary metabolites and their derivatives, and must be pure and highly characterized compounds. Originally, teas or decoctions (aqueous extracts) and tinctures or elixirs (alcoholic extracts) were used to prepare and administer herbal remedies. Nowadays different solvents are employed, for example, ethanol to extract, hexane to concentrate non-polar constituents, methanol to concentrate polar constituents, and modern isolation techniques include all types of chromatography, often guided by bioassays,

to isolate the active compounds. Structures are elucidated primarily by spectroscopic techniques and the stereochemistry is an important feature of the structure (Nyiredy, 2004).

A study by the World Health Organization (WHO) has shown that about 80% of the world's population still relies on traditional medicine (Farnsworth, 1985). However natural products still play an important role in the medicine of the remaining 20% because between 1981 and 2002, 52% of new approved drugs have natural products as their source. The percentage becomes even higher in the case of anti-infective and anti-cancer compounds, which increased over 60% (Newman & Cragg, 2007; Newman et al., 2003 and Cragg et al., 1997). This suggests that natural products are important sources for new drugs and are also good lead compounds suitable for further modification during drug development.

Natural products have the potential to provide medicine with a source of novel structures that are unobtainable from sources such as combinatorial synthesis. Nature is capable of producing complex molecules with multiple chiral centers that are designed to interact with biological system (Cordell, 2000). These compounds are often used by the producing organism as a self defense mechanism (da Rocha et al. 2001). The large proportion of natural products in drug discovery has stemmed from the diverse structures and the intricate carbon skeletons of natural products. Since secondary metabolites from natural sources have been elaborated within living systems, they are often perceived as showing more "drug-likeness and biological friendliness than totally synthetic molecules" (Koehn & Carter, 2005).

The treatment of diseases with pure pharmaceutical agents is a relatively modern phenomenon. Today, among 120 distinct chemical substances derived from plants that are widely being used in modern medicine today, 75 per cent show a positive correlation between their modern therapeutic use and the traditional use of the plants from which they are derived. Several of the drugs sold today are simple synthetic modifications or copies of the naturally obtained substances (Newman et al., 2003). Screening of both synthetic organic compounds and extracts of natural products has had an impressive history of identifying active agents. For example, there are about 50 commercially available anticancer drugs (excluding endocrines) which have been approved to date by the US FDA, and significantly, the drugs based on natural products represent almost one third of these total approved agents. A most recent addition is *taxol* (approved in 1992, and the semi-synthetic in 1995*),* a natural product derived from the Pacific yew tree *Taxus brevifolia,* which is used for the treatment of ovarian and breast cancer (Cragg et al., 1997).

In Malaysia, medicinal plants or herbs have long been used in the traditional medicine. Interests in herbs and herbal products have increased rapidly in recent years not only amongst scientists but also consumers. Efforts have been made to study in depth and document the use of herbs in this country. Amongst herbs given emphasis are Tongkat Ali (*Eurycoma longifolia* Jack), Kacip Fatimah (*Labisia pumila*), Mas Cotek (*Ficus deltoidea* Jack), Kerdas (*Pithecellobium bubalinum bent*) and Buah Keras or Candlenet (*Alleurites moluccana*). Some herbs were used as food or consumed as medicinal "ulam" or salads in Malaysia, whereas in other parts of the tropics, these herbs were dried and consumed in powdered form. Malaysians also

used "ulam" as preventive medicine and not as curative medicine, which made them very healthy.

Malaysia had started its journey into natural products research and this offered great potential for expansion. Nowhere else in the world was Asian traditional medicine better represented than in Malaysia, which was home to three systems of traditional medicine - Malay, Chinese and Indian. In 1999, when the Malaysian Industry-Government Corporation for High Technology (MiGHT) completed a study on the state of herbal industry, government officials and scientists were surprised that it had an annual sales value in excess of RM4 billion and also provided an excellent opportunity for employment. But up to 85 percent of the products were imported and this led to the setting up of MHC (Malaysian Herbal Council) to spur the growth of local herbal industry. Under the national biotechnology policy, ex-Prime Minister Datuk Seri Abdullah Ahmad Badawi stressed on the country's biotechnology agenda which includes niche developments in bio-pharmaceutical and bio-medicinal products (Daily Express, 25$^{th}$ April, 2005).

In this study, a pure compound extracted from one of the local medicinal plants, namely the *Zingiber zerumbet* (L) Smith was used to investigate its anti-leukemic properties. The compound is a sesquiterpene, known as zerumbone, was first screened for its cytotoxic effect with various types of cell lines including four different types of leukemic cell lines. However, the compound only showed a potent cytotoxic effect on leukemic cell lines tested compared to other cell lines. Therefore

the mechanism of its cytotoxic effect was investigated *in vitro* whereas its effectiveness and side effects as a potential antileukemic agent were evaluated *in vivo*.

So far there are two well known antileukemic drugs used in modern medicine, ie vinca alkaloids vincristine and vinblastine; originated from Madagascar's periwinkle plant *Cataranthus roseus* or locally known as *Kemuning Cina*. The vinca alkaloids are cell specific agents and block cells in mitosis with metaphase arrest. Their biological activity is explained by their specific binding to tubulin. Upon binding to vinca alkaloids, tubulin dimers are unable to aggregate to form microtubules (Pratt et al., 1994). This effectively decreases the pool of free tubulin dimers available for microtubule assembly, resulting in a shift of the equilibrium toward disassembly. Formation of paracrystalline aggregates by vinca-bound tubulin dimers shifts the equilibrium even further toward disassembly and microtubule shrinkage (Gupta & Bhattacharyya, 2003).

Leukemia is not a single disease; instead, the term refers to a number of related cancers that start in the blood-forming cells of the bone marrow. There are both acute and chronic forms of leukemia, each with many subtypes that vary in their response to treatment. Generally, there are five major approaches in the treatment of leukemia (Swierzewski, 2007):

1. Chemotherapy to kill leukemia cells using strong anti-cancer drugs;
2. Interferon therapy to slow the reproduction of leukemia cells and promote the anti-leukemia activity of the immune system;

3. Radiation therapy to kill cancer cells by exposure to high-energy radiation;
4. Stem cell transplantation (SCT) to enable treatment with high doses of chemotherapy and radiation therapy; and
5. Surgery to remove an enlarged spleen or to install a venous access device (large plastic tube) to give medications and withdraw blood samples.

## 1.2 The Importance Of The Study

The choice of this compound was based on several previous studies on zerumbone and strengthened by a lot of study on Zingiberaceae family (Cao et al., 2007; Mosley et al., 2007 and Shisodia et al., 2007). However, none has been reported extensively on cytotoxic and cell death mechanism of zerumbone on leukemic cell lines *in vitro.* This study also went further on the insight overview of zerumbone's effect on leukemic-induced mice, which has never been reported elsewhere. The information obtained could help in evaluating zerumbone's potential as an antileukemic agent and its side effects on major organs and blood parameter of the experimental animal.

## 1.3 Objectives

### 1.3.1 General objective

To study the potential of anti-leukemic properties of zerumbone extracted from *Zingiber zerumbet* plant.

### 1.3.2 Specific objectives

1. To evaluate the cytotoxic effect of zerumbone on different types of cancerous cell lines, including four types of leukemic cell lines and non-cancerous cells.
2. To assess zerumbone action on cell proliferation and cell cycle of WEHI-3B cells.
3. To identify the mode of cell death on zerumbone-treated WEHI-3B cell lines.
4. To investigate the effects of zerumbone on leukemic-induced mice.

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