UNIVERSITI PUTRA MALAYSIA

CHARACTERIZATION AND CYTOTOXICITY OF CLAUSENIDIN FROM Clausena excavata Burm f. AND ITS EFFECTS ON CELL CYCLE REGULATION AND APOPTOSIS OF LIVER (HEPG2) AND COLON (HT29) CANCER CELL LINES.

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By

PETER MAITALATA WAZIRI

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfillment of the Requirements for the Degree of Doctor of Philosophy

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DEDICATION

This work is dedicated first and foremost to God Almighty Whose grace and providence made this project a successful voyage. It is also dedicated to everyone who loves knowledge.

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfillment of the requirement for the degree of Doctor of Philosophy.

CHARACTERIZATION AND CYTOTOXICITY OF CLAUSENIDIN FROM *Clausena excavata* Burm f. AND ITS EFFECTS ON CELL CYCLE REGULATION AND APOPTOSIS OF LIVER (HEPG2) AND COLON (HT29) CANCER CELL LINES.

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February 2017

Chairman : Professor Rasedee Abdullah, PhD
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Clausena excavata Burm. *f*. is a wild shrub from the *Rutaceae* family predominantly found in tropical Asia. The plant is traditionally used in the treatment of cancers; however, its mechanism of anticancer action is still unknown. Among phytochemicals present in *C. excavata* are alkaloids, coumarins and limonoid. Clausenidin, a pyranocoumarin isolated from *C. excavata* is postulated to have anticancer effects. Thus, the objective of this study is to determine the *in vitro* anticancer effect of clausenidin on the liver (HepG2) and colon (HT-29) cancer cell lines.

The cytotoxicity and effect of clausenidin on the HepG2 and HT-29 cell cycles were determined via acridine orange/propidium iodide, reactive oxygen species (ROS), annexin V and cell cycle assays. DNA fragmentation and ultrastructural analyses, caspase-3 and -9 as well as MMP assays of the clausenidin-treated HepG2 and HT-29 cells were also performed to determine the mode of cell death. In addition, apoptosis-related genes and proteins were also analyzed using qPCR and Western blot respectively to further verify the effects of clausenidin on HepG2 and HT-29 cells.

The IC_{50} of clausenidin in HepG2 and HT-29 cells was 7.7 and 13.8 µg/mL at 72 hours of treatment, respectively. The results reveal that clausenidin induced G0/G1 and G2/M cell cycle arrest of HepG2 cells in a dose- and time-dependent manner. Clausenidin also caused depolarization of the mitochondrial membrane that resulted in the release of cytochrome C and significant ($p<0.05$) upregulation of Bax, Apaf-1, Smac, Caspase-3 and -9 proteins, suggesting involvement of the mitochondria pathway of apoptosis. It was also observed that the caspase-8, TNFR1, TRAIL, FADD and Fas proteins, which are key regulators of the extrinsic pathway of apoptosis were upregulated. Gene studies showed significant ($p<0.05$) increases in caspase-8 and -9 expression that further corroborates the involvement of the extrinsic and intrinsic

pathways in the apoptosis of clausenidin-treated HepG2 cells. The JNK, Bax, Apaf 1, cytochrome C, p53 and p21 genes were also found to be significantly ($p<0.05$) upregulated while Bcl-2, Bcl-x and HSP70 were downregulated. The findings suggest that clausenidin also suppressed the inducers of angiogenesis in HepG2 cells. Clausenidin-mediated apoptosis was evident by the increase in DNA fragmentation, typical microscopic and ultrastructural features of apoptosis.

Clausenidin induced responses in the HT-29 cells like that of the HepG2 cells, except that it did not cause significant ($p>0.05$) change in caspase-8, JNK and VEGF protein expressions. The HT-29 cells treated with clausenidin entered a G0/G1 cell cycle arrest. These cells also underwent depolarization of mitochondrial membrane resulting in cytochrome C release and subsequent increase in caspase-9 and Bax protein expressions that resulted in the activation of the intrinsic pathway of apoptosis. Clausenidin induced activation of caspase-3 that caused fragmentation of DNA and nuclei of the HT-29 cells, which are hallmarks of apoptosis. Upon treatment with clausenidin, HT-29 cells also showed increased production of ROS that is postulated to contribute to their death. The clausenidin-treated HT-29 cells like the HepG2 cells showed typical features of apoptosis although some cells underwent necrosis.

In conclusion, the study showed clausenidin isolated from *C. excavata* induced death of the HepG2 and HT-29 cells especially via apoptosis. Thus, clausenidin has the potential to be developed as a therapeutic compound for the treatment of liver and colon cancers.

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

PENCIRIAN DAN KESITOKSIKAN KLAUSENIDIN YANG DIEKSTRAK DARIPADA *Clausena excavata* Burm f. DAN KESANNYA TERHADAP PENGAWALATURAN KITARAN SEL DAN APOPTOSIS SEL KANSER HATI (HEPG2) DAN KOLON (HT29)

Oleh

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Pengerusi : Profesor Rasedee Abdullah, PhD
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Clausena excavata Burm. *f*. adalah pokok renek liar daripada keluarga *Rutaceae* yang kebanyakannya ditemui di Asia tropika. Tumbuhan ini digunakan secara tradisional untuk merawat kanser; walau bagaimanapun, mekanisme tindakan anti-kansernya masih belum diketahui. Antara fitokimia di dalam *C. excavata* adalah alkaloid, koumarin dan limonoid. Klausenidin, suatu piranokoumarin yang diasing daripada *C. excavata* dipostulat mempunyai kesan antikanser. Oleh itu, objektif kajian ini ialah untuk menentukan kesan antikanser klausenidin secara *in vitro*

Kesitotoksikan dan kesan klausenidin terhadap kitaran sel HepG2 dan HT-29 ditentukan melalui assai aridina jingga/propidium iodida, spesies oksigen reaktif (ROS), aneksin V, dan kitaran sel. Analisis penyepihan DNA dan ultrastruktur, dan assai kaspase 3 dan 9, dan MMP terhadap HepG2 dan HT-29 terperlaku klausenidin dilakukan juga untuk menentutkan cara kematian sel. Di samping itu, gen dan protein berkaitan apoptosis masing-masing dianalisis menggunakan qPCR dan sap Western untuk mengesahkan kesan klausenidin terhadap sel HepG2 dan HT-29.

Nilai IC_{50} klausenidin terhadap sel HepG2 dan HT-29 masing-masing adalah dengan 7.7 dan 13.8 µg/mL, selepas 72 jam perlakuan. Hasil kajian menunjukkan klausenidin mengaruh hentian kitaran sel pada fasa G0/G1 dan G2/M secara sandaran dos dan masa. Klausenidin juga menyebabkan penyahkutuban membran mitokondrion yang membawa kepada pembebasan sitokrom C dan peningkatan secara tererti ($p<0.05$) pengaturan naik protein Bax, Apaf -1, Smac, kaspase-3 dan -9 dan ini menyarankan penglibatan apoptosis arah laluan mitokondria. Peningkatan pengaturan naik protein kaspase 8, TNFR1, TRAIL, Fadd, dan Fas, yang merupakan pengatur utama apoptosis laluan ekstrinsik, telah juga dicerapkan. Kajian gen menunjukkan peningkatan tererti ($p<0.05$) dalam penyataan kaspase-8 dan -9 and ini lagi mengesahkan penglibatan

apoptosis laluan ekstrinsik dan intrinsik sel HepG2 terpelaku klausenidin. Pengaturan naik Gen JNK, Bax, Apaf 1, sitokrom C, p53, dan p21 didapati berlaku secara tererti ($p<0.05$) manakala Bcl-2, Bcl-x, dan HSP70 mengalami pengaturan turun. Hasil kajian menyarankan yang klausenidin juga menindas pengaruh angiogenesis pada sel HepG2. Apoptosis teraruh klausenidin jelas berlaku dengan peningkatan penyerpihan DNA, ciri mikroskopi and ultrastruktur apoptosis yang tipikal.

Klausenidin mengaruh gerak balas sel HT-29 sama seperti yang berlaku terhadap sel HepG2, kecuali ianya tidak menyebabkan perubahan tererti ($p>0.05$) dalam penyataan protein kaspase-8, JNK, dan VEGF. Sel HT-29 terperlaku klausenidin mengalami hentian fasa G0/G1 dalam kitaran selnya. Sel ini juga mengalami penyahkutuban membran mitokondrion yang menyebabkan pembebasan sitokrom C dan seterusnya peningkatan dalam penyataan protein kaspase-9 dan Bax yang membawa kepada pengaktifan arah lalaun intrinsik apoptosis. Klausenidin mengaruhkan pengaktifan kaspase-3 yang menyebabkan penyerpihan DNA dan nukleus sel HT-29, iaitu petanda pasti apoptosis. Apabila terperlaku klausenidin, sel HT-29 juga menunjukkan peningkatan pengeluaran ROS yang dipostulatkan sebagai penyumbang kepada kematiannya. Sel HT-29 terperlaku klausenidin seperti sel HepG2 menunjukkan ciri apoptosis yang tipikal walaupun sesetengahnya mengalami nekrosis.

Kesimpulannya, kajian ini menunjukkan klausenidin yang diasingkan daripada *C. excavata* mengaruh kematian sel HepG2 dan HT-29 khususnya melalui apoptosis. Oleh itu, klausenidin berpotensi untuk dibangunkan sebagai sebatian terapeutik untuk rawatan kanser hati dan kolon.

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I certify that a Thesis Examination Committee has met on 17 February 2017 to conduct the final examination of Peter Maitalata Waziri on his thesis entitled "Characterization and Cytotoxicity of Clausenidin from *Clausena excavate* Burm.f. and its Effects on Cell Cycle Regulation and Apoptosis of Liver (HepG2) and Colon (HT29) Cancer Cell Lines" in accordance with the Universities and University Colleges 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 fulfillment of the requirements for the Degree of Doctor of Philosophy. The members of the Supervisory Committee were as follows:

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Bax	Bcl-2 associated protein
Bcl-2	B-cell lymphoma 2
CAD	Caspase activated DNase
CDK	Cyclin dependent kinase
DIMS	Direct Infusion Mass spectra
DMSO	Dimethyl sulphoxide
DNA	Deoxyribonucleic acid
EDTA	Ethylene diamine tetraacetic acid
FITC	Fluorescene isothiocyanate
HepG2	Human hepatocellular carcinoma
HT-29	Human adenocarcinoma cells
HSP	Heat shock proteins
IC_{50}	Inhibitory concentration (50%)
MMP	Mitochondrial Membrane Potential
mRNA	Messenger Ribonucleic acid
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
NMR	Nuclear Magnetic Resonance
OD	Optical density
PBS	Phosphate Buffered Saline
ROS	Reactive oxygen species
TAE	Tris acetate EDTA
Tris-HCl	Tris hydrochloric acid
TLC	Thin Layer Chromatography
VEGF	Vascular endothelial growth factor

CHAPTER ONE

INTRODUCTION

1.1 Overview of *Clausena excavata* Burm. *f*.

Clausena excavata Burm *f*. is a wild medicinal shrub from the *Rutaceae* family. It is locally known as *Chemen* or *Cherek Hitam* in Malaysia and *San Soak* in Thailand (Descola and Pálsson, 1996; Khare, 2008). *Clausena* is a genus of 14 species predominantly found in Tropical Asia (Shier, 1983; Arbab *et al.*, 2012). In Thailand, the extracts of *Clausena excavata* is used for the treatment of cancers. The use of this plant in traditional medicine is based on hearsay and previous experience and with little or no scientific evidence supporting its therapeutic uses. The phytochemistry of *C. excavata* are currently being extensively studied and many secondary metabolites that are beneficial to health have been identified through various extraction and identification techniques (Zhi, 2006; Kongkathip *et al.*, 2010; Arbab *et al.*, 2013). Coumarins, alkaloids and limonoids are among the most abundant natural products in *C. excavata*. Recently, the effect of the extracts of *C. excavata* and some of its compounds were determined *in vitro* on a panel of cancer cell lines (Wu *et al*., 1994; Ali *et al*., 2000; Su *et al.*, 2009). Clausenidin is one of the compounds identified as an anti-cancer agent that contributes to the therapeutic effect of *C. excavata*. However, the mechanism of action of clausenidin is still unknown.

1.2 Common cancers affecting man

Cancer is a group of diseases characterized by uncontrolled cell growth and division and formation of tumors that invade and destroy tissues. The disease is a global problem and affects quality of life (Connolly and Rose, 1998). Based on WHO reports, the number of cancer deaths worldwide exceeds that from coronary heart disease and stroke combined together (Society, 2013).

The rate of increase in cancer cases is alarming and by the GLOBOCAN's estimates, in 2012 over 14 million cancer cases have been diagnosed, of which 8 million deaths were mainly the result of lung, breast, liver and colon cancers (Ferlay *et al.*, 2013). The cost of management of cancer amounts to approximately USD125 billion globally in 2010 and it is projected to increase to USD158 billion by year 2020 (Jemal *et al.*, 2004). Cancer management is costly, as such, cancer therapy remains an exclusive privilege of the well-developed and wealthy nations of the world. Ministry of Health of Malaysia reported that malignant neoplasms constitute the third major leading cause of death in Peninsular Malaysia (Omar *et al.*, 2006). The situation is even worse in Africa where cancer burden is expected to increase by 85% by the year 2030 (Morhason-Bello *et al.*, 2013).

Liver and colon cancers are peculiar to Africa and Malaysia, respectively. Liver cancer usually appear in form of hepatocellular carcinoma (HCC), hepatoblastoma, or

cholangiocarcinoma (Jemal *et al.*, 2009). The cancer more often affects men than women (Society, 2013). Among the causes of liver cancers is chronic viral hepatitis. Liver cancers, like other cancer are treated by surgery, radiotherapy and chemotherapeutic drugs.

Colon cancer cases are also on the increase worldwide. The cancer is also known as colorectal cancer because carcinomas of the colon and rectum have similar pathology. Over 95% of colon cancers are adenocarcinomas (Society, 2013). Among major risk factors to colon cancer are diet, age and unhealthy lifestyle. Survivability from colon cancers is poor because there is no single efficient method that could be used to permanently remove the cancer tissues.

1.3 Anticancer compounds of plant sources

According WHO reports, 80% of the world's population depend largely on plant-based traditional medicine (Newman *et al.*, 2003; Koehn and Carter, 2005). These medicinal plants contain phytochemicals and nutrients and while curing diseases are also nutritious (Taylor *et al.*, 2001; Krief *et al.*, 2005). Historically, plants are the oldest and most sought sources of chemotherapeutic compounds. Currently, there are an estimated 200,000 to 500,000 plant species; some of which are potential sources of therapeutic compounds (Raven, 1988; Borris, 1996). Less than 10% of these plants are consumed as food and approximately 20% are being used for therapeutic purposes (Moerman *et al.*, 1996). Some herbs and plants were shown to be effective in the treatment of early stage cancers (Cragg and Newman, 2005). About 115,000 plant extracts from over 30,000 plant species globally have been screened for their anticancer properties by the United States National Cancer Institute (Shoeb, 2006; Tan and Zhou, 2006).

In tropical Asia, *Clausena excavata* Burm *f.* is commonly used for the treatment of different ailments. The use of this plant is an ancient folklore that is still practiced to date. About four pyranocoumarins were isolated from *C. excavata* and their effect on cancers were determined *in vitro* on a panel of cancer cell lines (Su *et al.*, 2009). Among these pyranocoumarins is clausenidin that was postulated to have anti-cancer properties. In our study, clausenidin was extracted from fresh roots of *C. excavata* and purified to its crystalline form. To determine the potential of clausenidin as an anticancer agent, its effects were investigated *in vitro* using the liver (HepG2) and colon (HT-29) cancer cell lines.

1.4 Research problem

Current chemotherapeutic drugs are plagued with undue side-effects and eventual development of drug-resistance. The anticancer drug currently in use are expensive and not affordable by people of low income groups of which the majority are in underdeveloped and developing countries.

1.5 Hypothesis

1.5.1 Null Hypothesis

Clausenidin is not cytotoxic to cancer cells.

1.5.2 Alternate Hypothesis

Clausenidin from *C. excavata* is a potent inhibitor of tumor cell growth and cancer spread through the production proteins of the apoptosis pathways.

1.6 Objective

The general objective of the study is to evaluate the cytotoxic and anti-proliferative effects of clausenidin on liver and colon cancer cell lines. The specific objectives are to:

1. characterize clausenidin isolated from *Clausena excavata*.
2. determine the cytotoxic effects of clausenidin on the HepG2 and HT-29 cell lines *in vitro*.
3. determine the effects of clausenidin on genes and proteins involved in the regulation of cell cycle and apoptosis of the HepG2 and HT-29 cells.
4. determine the pathways involved in the death of HepG2 and HT-29 cells induced by clausenidin.

1.7 Justification

At present, cancer is synonymous with death sentence because of the devastating consequences of the disease. It is projected that by the year 2030, 17 million people would have died of cancers. The significant majority of cancer cases and deaths are expected to be in Asia and Africa, where good and structured health care and services are not in place. The cost of treatment and management of the disease is enormous, especially with the use of costly modern drugs. In addition, modern drugs have deleterious effects that can lower quality of life of cancer patients.

Therapeutic compounds from natural sources are not only in abundance but also cheap to produce. Cheap drugs and compounds will benefit poor societies either by extending life of cancer patients or improving quality of life. Thus, the discovery of natural anticancer compounds may alleviate the sufferings from this debilitating disease.

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