UNIVERSITI PUTRA MALAYSIA

EXTRACTION, CHARACTERISATION, OPTIMISATION AND MODELING OF PHALERIN FROM PHALERIA MACROCARPA (SCHEFF.) BOERL LEAVES

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EXTRACTION, CHARACTERISATION, OPTIMISATION AND MODELING OF PHALERIN FROM *PHALERIA MACROCARPA* (SCHEFF.) BOERL LEAVES

By

NOR FARIZA ISMAIL

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

November 2014

This thesis is specially dedicated to
my beloved husband Hafidz,
my wonderful kids Haikal, Harith and Haziq Irfan,
my parents
and
my in laws.

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

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November 2014

Chairman : Professor Luqman Chuah Abdullah, PhD.
Faculty : Engineering

Phaleria macrocarpa (Scheff.) Boerl is a medicinal plant found in Malaysia and Indonesia. This plant has been used traditionally to treat various diseases. Little studies have been done to identify compound that contributes to medicinal effect. Moreover, there is lack of studies in the method to extract those valuable components from this plant.

This research focuses on the leaves part of the plant. A single compound known as phalerin is targeted and extracted from the leaves. The compound is purified and identified through chemical analysis such as High Performance Liquid Chromatography, Thin Layer Chromatography, Nuclear Magnetic Resonance and Liquid Chromatogram Mass Spectroscopy. Phalerin was tested for the bioactivity study including antioxidant, anti-inflammatory and anticancer. Then the extraction process using solid-liquid extraction method was investigated on the optimum parameters; solvent, extraction temperature, solid-to-solvent ratio and particle size.

Phalerin was proven having antioxidant and anti-inflammatory activity. Water was the most suitable solvent for extraction of phalerin from the leaves compared to methanol, ethanol, ethyl acetate and hexane. Water was not only safe but also extracted most of polar compounds. The optimum temperature was at 70°C as to avoid degradation of compound. The optimum solid to solvent ratio was 1:20 (g/ml) as too much solvent leads to waste of solvent and extra energy to remove excess liquid. The smallest particle size (<250 μm) was the optimum size as smaller particle provide larger surface area for mass transfer.

Extraction kinetics on extraction of phalerin found that the process reach equilibrium at 120 min of extraction duration. The first order kinetics model was applied and successfully described the extraction process. From thermodynamic study, the enthalpy change (ΔH) was found to be positive (72.51 kJ/mol), indicating the extraction process of *Phaleria macrocarpa* leaves is endothermic. The Gibb's free energy was found to be negative with values range from -2.75 to -9.95 kJ/mol, indicated the extraction was spontaneous at the operating temperature. This spontaneity was favored with increasing extraction temperature.

Phalerin is a bioactive compound extracted from *Phaleria macrocarpa* leaves and having antioxidant and anti-inflammatory activities. Standardization of extract and improvement on the extraction process along with clinical study of phalerin may added new information to this study.

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

PENGEKSTRAKAN, PENCIRIAN, PENGOPTIMUMAN DAN PEMODELAN PHALERIN DARI DAUN *PHALERIA MACROCARPA* (SCHEFF.) BOERL

Oleh

NOR FARIZA ISMAIL

November 2014

Pengerusi : Profesor Luqman Chuah Abdullah, PhD.
Fakulti : Kejuruteraan

Phaleria macrocarpa (Scheff.) Boerl adalah tanaman bernilai yang boleh didapati di Malaysia dan Indonesia. Tumbuhan ini telah digunakan secara tradisional untuk merawat pelbagai penyakit. Hanya terdapat sedikit kajian yang telah dijalankan untuk mengenalpasti kandungan bahan yang menyumbang kepada kesan perubatan. Tambahan lagi, masih kurang penyelidikan terhadap kaedah untuk mengekstrak kandungan bahan yang bermanfaat dari tumbuhan ini.

Kajian ini tertumpu kepada bahagian daun pada tumbuhan. Satu kandungan bahan yang dikenali sebagai phalerin telah disasarkan dan diekstrak daripada daun. Kandungan bahan ini telah dikenalpasti melalui analisis kimia seperti *High Performance Liquid Chromatography*, *Thin Layer Chromatography*, *Nuclear Magnetic Resonance* dan *Liquid Chromatogram Mass Spectroscopy*. Phalerin telah dikaji untuk tindakan biologi termasuk antioksida, anti radang dan anti kanser. Kemudian, proses pengekstrakan menggunakan kaedah pengekstrakan pepejal-cecair telah dikaji terhadap parameter yang optimum iaitu pelarut, suhu pengekstrakan, nisbah pepejal-cecair dan saiz bahan.

Phalerin telah disahkan mengandungi antioksida dan anti radang efek. Air dikenalpasti sebagai pelarut yang paling sesuai untuk mengekstrak phalerin daripada daun berbanding dengan metanol, etanol, etil asetat dan heksana. Air bukan sahaja selamat tetapi mampu mengekstrak bahan-bahan bersifat polar. Suhu optimum adalah pada 70°C untuk mengelakkan degradasi bahan. Nisbah pepejal kepada cecair yang optimum adalah 1:20 (g/ml) kerana bahan pelarut yang banyak boleh menyebabkan pembaziran dan juga memerlukan tenaga yang lebih untuk diasingkan. Saiz bahan yang paling kecil iaitu <250μm adalah yang optimum kerana saiz yang lebih kecil memberi luas permukaan yang lebih besar untuk process pertukaran bahan.

Pengekstrakan phalerin melalui kajian kinetik pengekstrakan mendapati proses ini mencapai *equilibrium* pada 120 min. Model *first order kinetics* telah diaplikasi dan berjaya menerangkan proses pengekstrakan. Daripada pengkajian termodinamik, perubahan entalpi didapati positif dengan nilai 72.51 kJ/mol dan ini menerangkan proses pengekstrakan daun *Phaleria macrocarpa* adalah endotermik. *Gibb's free*

energy didapati negatif dengan nilai dari -2.75 hingga -9.95 kJ/mol yang menerangan proses kinetik berlaku secara spontan pada suhu yang dijalankan. Proses yang spontan ini berlaku berkadaran dengan peningkatan suhu.

Phalerin merupakan compound aktif yang diekstrak dari daun *Phaleria macrocarpa* dan mengandungi aktiviti anti oksida dan anti radang. Penyeragaman ekstrak dan menambahbaikan dalam proses pengekstrakan serta kajian perubatan terhadap phalerin boleh memberi maklumat baru dalam kajian ini.

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I certify that a Thesis Examination Committee has met on 11th November 2014 to conduct the final examination of Nor Fariza Ismail on her thesis entitled "EXTRACTION, CHARACTERISATION, OPTIMISATION AND MODELING OF PHALERIN FROM *PHALERIA MACROCARPA (*SCHEFF.) BOERL LEAVES" 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 requirement of the degree of Doctor of Philosophy. The members of the Supervisor Committee are as follows:

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A	Arrhenius constant
A_0	Absorbance of negative control
ABTS	2,2-azinobis (3-ethylbenzothiazoline-6-sulfonic acid)
A_c	Absorbance of control
A_{ref}	Absorbance of reference
A_s	Absorbance of test material
A_T	Area of solid liquid interface (m^2)
a	Interfacial surface area (cm^{-1})
C_A	Concentration of solute in the solid phase (kg/m^3)
C_C	Concentration of solute C in the solution (kg/m^3)
CC	Column chromatography
CD_3OD	Deuterated methanol
C_e	Concentration of solute at equilibrium
CE	Capillary electrophoresis
C_e^{d1}	Concentration at equilibrium in diffusion step 1
C_e^{d2}	Concentration at equilibrium in diffusion step 2
C_e^w	Concentration at equilibrium in washing step
CH	Carbon-hydrogen bond
CH_2	Methylene
CH_3CN	Acetonitrile
CNMR	Carbon nuclear magnetic resonance spectroscopy
CO_2	Carbon dioxide
C_s	Concentration of solute at saturation or equilibrium (mgL^{-1})
C_t	Concentration of solute at any time t
D	Diffusivity of the solute in the solvent or inert solid (m^2/s)
D_{eff}	Effective diffusivity
DCM	Dichloromethane
DEPT	Distortionless enhancement by polarization transfer
DMSO	Dimethylsulfoxide
DPPH	2,2-diphenyl-1-picrylhydrazyl
E	Mean relative deviation modulus
h	Initial extraction rate
h'	Plank constant (6.626×10^{-34} J.s)
H_2O	Water
HNMR	Hydrogen nuclear magnetic resonance spectroscopy
HPLC	High performance liquid chromatography
HYA	Hyaluronidase
IR	Infrared spectroscopy
IUPAC	International Union of Pure and Applied Chemistry
k	Rate constant
K_1	First order rate constant (min^{-1})
K_2	Second order rate constant ($ml\ g^{-1}min^{-1}$)
K	Equilibrium constant
ka	Volumetric mass transfer coefficient

k_{d1}	Mass transfer coefficient of diffusion step 1 (min^{-1})
k_{d2}	Mass transfer coefficient of diffusion step 2 (min^{-1})
k_w	Mass transfer coefficient of washing step
LOX	Lipoxygenase
M	Mass (g)
MeOH	Methanol
MS	Mass spectroscopy
MTT	3-(4,5-Dimethylthiazol-2-Yl)-2,5-Diphenyltetrazolium Bromide
N	Avogadro number
N_c	Rate of dissolution of solute C in the solution (kg/s)
NDGA	Nordihydroguaiaretic acid
NMR	Nuclear magnetic resonance spectroscopy
OCH_3	Methoxy group
PVDF	Polyvinylidene fluoride
r	Distance from the solid center (cm)
R	Gas constant (8.314 J/mol.K)
R^2	Correlation coefficient
R_f	Retention factor
RMSE	Root mean square error
SLE	Solid liquid extraction
t	Time (min)
TEAC	Trolox equivalent antioxidant capacity
TLC	Thin layer chromatography
UV-Vis	Ultraviolet visible spectroscopy
V	Volume
V_e	Volume of extract used for freeze drying (ml)
V_t	Volume of extract obtained after filtration (ml)
W_d	Weight of dried extract (g)
W_s	Weight of dried solid leaves (g)
X	Distance
XO	Xanthine oxidase
Y_T	Percent phalerin extracted at equilibrium
Y_U	Percent unextracted phalerin at equilibrium
Z	Distance inside the porous of the solid matrix (m)
ΔG	Gibb's free energy (kJ/mol)
$\Delta G^{\neq}$	Activation free energy (kJ/mol)
ΔH	Enthalpy change (kJ/mol)
$\Delta H^{\neq}$	Activation enthalpy (kJ/mol)
ΔS	Entropy change (J/mol.K)
$\Delta S^{\neq}$	Activation entropy (J/mol.K)
ε	Void fraction space or porosity of the solid
λ_n	Eigenvalues
ρ_A	Density of solid (gcm^{-3})
τ	Dimensionless time

CHAPTER 1

INTRODUCTION

1.1 Background

Traditional medicine is the sum of total knowledge, skills, practices based on theory, beliefs and experiences indigenous to different culture, whether explicable or not, used in diagnosis, prevention and elimination of physical, mental or social imbalance (WHO Traditional medicine Programme, See Zhang, 1998). Traditional medicine is being used globally and it is estimated over 64% of world's population rely on plants as a primary health care source. Traditional medicine is relatively healthier, holistic, promote health and life quality and more self-reliance.

World population nowadays is increasingly seeking natural, drugless remedies or solutions to health problems. Moreover, considerable attention has been paid to utilize eco-friendly and natural based product for the prevention and cure of human diseases. Traditional medicine, based on natural product, is highly lucrative in the international medicine where it covers various aspect including photochemical, drugs, extracts, essential oils, nutraceuticals and aromatherapy. With such amount of diverse application of natural product, the demand for it shows increment of 5 to 13 percent annually. The largest market of the natural product in the world is in Europe followed by United State, Asia, Japan and other countries. In America, the spending on the complementary and alternative medicine industry in 2007 was approximately $34 billion by which $18 and $4 billion of this overall expenditure represented dietary supplements and herbal products respectively (National Center for Complementary and Alternative Medicine, 2013). In Malaysia, traditional medicine has penetrate the herbal industry due to its rewarding business by which the per capita consumption of traditional medicine products is more than double the consumption of modern pharmaceuticals.

Among the common herbs being used as traditional medicine in Malaysia are ginger (*Zingeber officinale*), garlic (*Allium sativum*), turmeric (*Curcuma Longa*), piper (*Piper betle L.*), *Centella asiatica* L., *Orthosiphon staminus* and *Eurycoma longifolia*. Most of these common herbs are used traditionally to treat general illness such as flu, fever, allergies and dysentery due to antibacterial, anti-inflammatory, antioxidant and antidiabetic activities (Anand et al., 2010; Bhat & Karim, 2010; Ho et al., 2010; Mesomo et al., 2013; Pin et al., 2010; Singh et al., 2010). Besides aiming for treating certain illnesses, natural herbs have been taken regularly as healthy drink, tea, coffee and salad (Joubert & de Beer, 2011). The old folks' practices are the main sources for the growth of today's products which based on the natural resources and claim for having specific medicinal effects. However, with the increasing demand for natural product, precaution has to be taken seriously to ensure the products available are efficacious, of quality and safe for human use.

Studies on traditional medicine have been conducted to investigate the efficacy of the herbs practices from generation to generations. Normally, the traditional medicine practices on ordinary herbs that can easily be found in backyard. For example, turmeric or *Curcuma longa* which is a common ingredient in Malaysian cuisine has been identified having antioxidant, antiviral, antifungal, anti-inflammatory and anticancer activities through recent studies. Thus, with supporting information from various discipline regarding natural herbs, an emerging supply and demand for natural product is flocking the market. With that, each party such as medical profession, investigative scientists, regulatory agencies and public have to understand the particular characteristics of natural herbs and derivatives and their potential for success and failure in preventing and confronting diseases (Barnes & Prasain, 2005).

Herbal processing industry is a team to develop natural product which started from the collection of raw product, pretreatment, extraction and finally provide product to the consumer for further usages or applications as shown in Figure 1.1. This process is a part of larger industry incorporating the pharmaceuticals, nutraceuticals, functional foods, herbal remedies and nutritional supplements. In herbal processing industry, extraction oil, bioactive ingredients, aroma or flavor are among the products that are valuable in the market. Thus, a process development in producing these valuable natural products is essential to ensure the herbal product met the quality, safety and efficacy requirements.

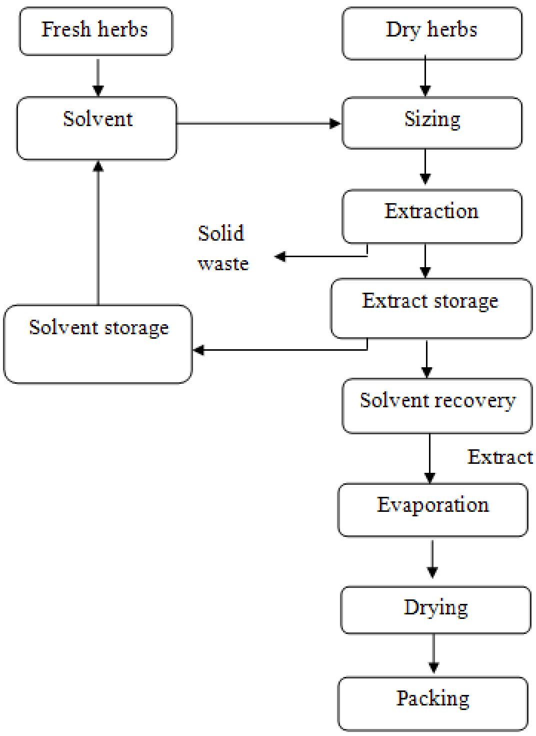

Figure 1.1: Herbal processing flow diagram

1.2 *Phaleria macrocarpa* (Scheff.) Boerl

Phaleria macrocarpa (Scheff.) Boerl shown in Figure 1.2 is a plant originally found in Indonesia. It is known by the name of Mahkota dewa (God's crown) in Malaysia and Indonesia. Most parts of this plant have been used to treat various diseases by the old folk Indonesians. All parts including the fruit, leaves, stem and seed have been studied extensively to determine the usages based mainly on the old folk practices. The seed of this plant is toxic to be consumed and thus only be used topically. This is due to the toxicity exhibited by the plant which might cause burning and numb effect if consume without any pretreatment.

Figure 1.2: *Phaleria macrocarpa*

This plant grows in fertile soil at an altitude of 10-1200 meters above sea level. It becomes productive after an age of about 4 months and can be utilized for 10 to 20 years. It can be found in tropical climates and reaches 1-2.5 meters in height in cultivation and up to 6 meters in wild.

Traditionally, this plant has been consumed for allergy, dysentery, skin diseases and energy drink. From the recent studies, *Phaleria macrocarpa* has been identified as a potential plant source which provides biological activities to treat or prevent certain diseases. Among chemical constituents found in the leaves, fruits and the pericalp are alkaloids, saponin, polyphenols, tannins, flavonoids, phenol and sterols (Harmanto, 2003). Moreover, these parts of plant are proven having antioxidant, anticancer, antidiabetic and anti-inflammatory activities.

1.3 Problem statement

Traditional medicine or alternative medicine is widely used in the prevention, diagnosis and treatment of an extensive range of ailments. The facts that the traditional medicine is easily accessible which commonly found in the backyard, affordable and not require complicated process to consume make it as first remedies rather than the modern medicine to certain people.

Phaleria macrocarpa is one of the medicinal plants that recently penetrate the herbal industry in Malaysia. This plant consists of stem, fruits, leaves, and seed, has multiple medical usages. Through recent studies the stem has potential in treating bone cancer (Hendig & Ermin, 2009), the fruits can treat tumor, the leaves can treat allergy while the seed not only toxic but can be used for skin diseases (Faried et al., 2007). Eventhough the *Phaleria macrocarpa* plant has proven having various medicinal purposes but little findings has done to identify the compounds in the plant that contribute to those effects.

Many studies focused on the constitution of *Phaleria macrocarpa* and the efficacy of the crude extract of *Phaleria macrocarpa* on the certain diseases. However, there is lack of linkage between these two by which on how the compound that contribute to treat certain diseases can be obtained at optimal condition using extraction process. *Phaleria macrocarpa* is reported to contain phalerin which contributes to the anti-inflammatory and cytotoxic effect. Phalerin is not only major but also active compound that can be found only in the leaves of *Phaleria macrocarpa*. Thus, this study focuses on optimum parameters of extracting phalerin from the plant by solid liquid extraction method. Since phalerin standard was not available for the study, the method of extracting phalerin needs to be performed. The characterisation of phalerin obtained is compared and confirmed with previous study done by Mae et al. (2005).

From recent studies, *Phaleria macrocarpa* has been identified as a potential plant source which provided biological activities to treat or prevent certain diseases. However, there is still some area that is needed to study even further. This study focuses on the bioactivity of the extracted compounds that exhibit the biological activity such as antioxidant, anti-inflammatory and anticancer. Upon identifying the active compound, a study to optimize the extraction parameters subject to the active compound is performed. Conventional solid liquid extraction process is commonly used in herbal industry due to it simple process and require less equipment. Therefore, this method is used in this study. Kinetics study of process is then investigated.

1.4 Objectives of the study

The main objective of the study is to identify an active component from the leaves that contribute to the biological effect of the plant and proposed the optimum process parameters that could produce high yield of that compound. Moreover, it provided some useful information on the usages and the related parameters when dealing with the extraction process of this plant.

The study aims for the followings:

1. To identify the characteristics of extracted compound from the *Phaleria macrocarpa* leaves known as phalerin through chemical analysis.

2. To investigate the bioactivity of the extracted compounds through in-vitro study using antioxidant, anti-inflammatory and anticancer assays.
3. To optimize process parameters including type of solvents, ratio of solid to solvent, solid particle size and temperature for solid liquid extraction of *Phaleria macrocarpa* leaves.
4. To investigate extraction kinetics of active compound from *Phaleria macrocarpa* leaves and applied mathematical models for solid liquid extraction of the leaves.

1.5 Scope of the study

This study focuses on the extraction process of *Phaleria macrocarpa* leaves. The leaf has not been studied extensively and thus there is no study yet done on the optimization and kinetics of the extraction process. The findings are supported by the bioactivity related to the single compound extracted.

The extraction process of *Phaleria macrocarpa* leaves initially was focusing in identifying the single component that is major and has medicinal effect. The extraction was carried out through solid liquid extraction. Extraction and fractionation process was done to isolate a single compound from the leaves. High Performance Liquid Chromatography (HPLC), Thin Layer Chromatogram (TLC), Nuclear Magnetic Resonance (NMR) and Liquid Chromatogram Mass Spectroscopy (LCMS) were performed to ensure a single component was extracted and determined the identity of particular compound based on literature. Later, the obtained component was tested for antioxidant, anti-inflammatory and anticancer effect.

The optimization of extraction process was carried out using solid-liquid extraction method. Through this study, type of solvent, particle size, extraction temperature and solid-to-solvent ratio was optimized based on the crude yield and the phalerin concentration. The HPLC was used to determine the concentration of phalerin present in the extract. Moreover, the effect of each extraction parameters on the yield and concentration of phalerin was studied. The solvent effect on the yield was carried out and the reasons for having such solvent was rectified to ensure high quality and quantity of extract was obtained besides the safety requirement for food processing methods. The practical particle size and solid-to-solvent ratio was measured for the optimum yield. Moreover, consideration of waste due to solvent was measure for choice of solid-to-solvent ratio. On the other hand, optimum parameters were evaluated based on yield obtained and the quality of the phalerin present in the extract.

Based on the optimization process, the kinetics study was performed using lab scale solid-liquid extractor. The process was performed until the system reached equilibrium. Mathematical models were proposed to predict the extraction process.

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