OPTIMIZATION AND FRACTIONATION OF QUERCITRIN-RICH EXTRACT FROM *MELASTOMA MALABATHRICUM* LEAVES AND ITS BIOACTIVITIES

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A thesis submitted in fulfilment of the
requirements for the award of the degree of
Doctor of Philosophy

School of Chemical and Energy Engineering
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Dedicated to my beloved parents, family, lecturers and last but not least my fellow friends

ACKNOWLEDGEMENT

In the name of Allah s.w.t and Rasullulah s.a.w, I would like to grant my utmost gratitude to ALLAH the almighty for without the consent, inspiration and help, this study would have not been completed successfully.

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ABSTRACT

Melastoma malabathricum (*M. malabathricum*) is also known as "senduduk". It is a small shrub belonging to the family *Melastomaceae.* According to scientific studies, the leaves of this plant have been proven to possess many beneficial bioactivities and its extract has great therapeutic potential. However, limited research has been carried out, especially on the processing technologies for the bioactive extract of *M. malabathricum* leaves. Therefore, this study focused on the effect of temperatures on the drying kinetics and quality of *M. malabathricum* leaves in determining the optimum drying temperature. Degradation of quercitrin above 50^oC suggesting that this could be the optimum temperature ranges. Midilli et al model shows to have the best fit to the experimental data of drying among the selected thin layer models with the high correlation coefficient (R^2>0.98). Response surface methodology was employed to optimize the ultrasonic assisted extraction and solid phase fractionation processes of *M. malabathricum* leaves using central composite design. The optimized extraction process conditions were solid to solvent ratio (1 mg: 20.83 ml), ultrasonic amplitude (68.6%) and particle size (440 µm) to obtain 13.4 % yield. The optimized fractionation conditions were loading concentration of crude extract (9.13 mg/ml), ratio of eluent system (70.4 %, methanol) and volume of eluent system (18.24 ml). The result showed that the content of quercitrin was increased from 10.31 mg/g in crude extract to 36.02 mg/g after fractionation using solid phase extraction (SPE). An equilibrium dependent extraction (EDE) model has successfully applied in describing the extraction process. EDE model is more accurate with R^2 value more than 0.90 and root mean square error less than 0.001. This explains the mass transfer resistance caused by quercitrin diffusion is negligible. The anti-diabetic activity of samples was successfully determined using dipeptidyl peptidase IV assay *in vitro* and *in silico*. The IC_{50} of extract and fraction were found to be 48.25µg/ml and 30.71µg/ml, respectively. The lower IC_{50} of fraction revealed the higher anti-diabetic activity of the fraction than crude extract. The binding energy of quercitrin was -6.21 kcal/mol which means the lowest of binding energy has high potential on anti-diabetic activity. The processing technology of quercitrin rich extract from *M. malabathricum* has been established based on the ultrasonic assisted extraction and followed by SPE clean-up process.

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Melastoma malabathricum (*M. malabathricum*) juga dikenali sebagai "senduduk". Ia adalah sejenis pokok rimbun yang berasal daripada keluarga *Melastomaceae*. Menurut kajian saintifik, daun tumbuhan ini telah terbukti mempunyai banyak bioaktiviti yang bermanfaat dan ekstraknya mempunyai potensi terapeutik yang besar. Walau bagaimanapun, kajian yang telah dijalankan adalah terhad, terutamanya dalam teknologi pemprosesan ekstrak bioaktif daun *M. malabathricum*. Oleh itu, kajian ini memberi tumpuan kepada kesan suhu pada kinetik pengeringan dan kualiti daun *M. malabathricum* dalam menentukan suhu pengeringan optimum. Perosotan quercitrin melebihi 50^oC boleh dicadangkan sebagai julat suhu optimum. Midilli et al model menunjukkan yang paling sesuai untuk data eksperimen pengeringan di antara model lapisan nipis dengan pekali korelasi tinggi (R^2>0.98). Kaedah sambutan permukaan digunakan untuk mengoptimumkan proses pengektrakan berbantu ultrasonik dan pecahan fasa pepejal daun *M. malabathricum* menggunakan rekabentuk komposit berpusat. Keadaan proses pengekstrakan yang optimum adalah nisbah pepejal kepada pelarut (1 mg:20.83 ml), amplitud ultrasonik (68.6%) dan saiz nisbah zarah (440 µm) untuk mendapatkan hasil 13.4%. Keadaan pecahan yang dioptimumkan ialah pemuatan kepekatan ekstrak mentah (9.13 mg/ ml), nisbah sistem eluen (70.4%, metanol) dan isipadu sistem eluen (18.24 ml). Keputusan menunjukkan bahawa kandungan quercitrin meningkat dari 10.31 mg/g dalam ekstrak mentah hingga 36.02 mg/g selepas menggunakan pengekstrakan fasa pepejal (SPE). Model pengekstrakan bergantung keseimbangan (EDE) telah berjaya diterapkan dalam menerangkan proses pengekstrakan. EDE model ini lebih tepat dengan nilai R^2 lebih daripada 0.90 dan kesilapan punca-min-kuasadua kurang daripada 0.001. Ini menjelaskan rintangan pindah jisim yang disebabkan oleh penyerapan quercitrin diabaikan. Aktiviti anti-diabetes sampel telah berjaya ditentukan menggunakan assay dipeptidil peptidase IV *in vitro* dan *in silico*. IC_{50} ekstrak dan pecahan masing-masing didapati 48.25µg/ ml dan 30.71µg / ml. Pecahan IC_{50} yang lebih rendah mendedahkan aktiviti anti-diabetes yang lebih tinggi daripada pecahan berbanding ekstrak mentah. Tenaga ikatan yang mengikat quercitrin ialah -6.21 kcal /mol ini bermakna tenaga ikatan yang rendah mempunyai potensi tinggi terhadap aktiviti anti-diabetes. Teknologi pemprosesan ekstrak kaya quercitrin dari *M. malabathricum* telah ditubuhkan berdasarkan pengekstrakan berbantu ultrasonik dan diikuti oleh proses pembersihan SPE.

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TPC	-	Total phenolic content
TFC	-	Total flavonoid content
DPPH	-	Free radical scavenging
SPE	-	Solid phase extrcation
DPP-IV	-	Dipeptdyl peptidase-IV

LIST OF SYMBOLS

b_o	-	Regression coefficient of intercept term
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DECLARATION

"I declare that this thesis entitled Optimization and Fractionation of Quercitrin-rich Extract from *Melastoma malabthricum* Leaves and Its Bioactivities" is the result of my own research except as cited in the references. The thesis has not been accepted for any degree and is not concurrently submitted in candidature of any other degree.

Signature : ....

Name : MOHD AZRIE BIN AWANG

Date : 30th APRIL 2019

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CHAPTER 1

INTRODUCTION

1.1 Research Background

Nowadays, there has been an increasing demand for specialty phytochemicals in herbal medicinal products, cosmeceuticals, neutraceuticals and functional food products. This trend is somewhat due to the consumer preference for products containing phytochemical ingredients, which are generally perceived as milder, safer and healthier than their synthetic equivalents (Harjo *et al.*, 2004). In addition, medicinal plants have formed the basis of traditional medicine system, and more recently are good sources of lead compounds for modern medicines, neutraceuticals, food supplements, folk medicines, pharmaceutical intermediates and chemical entities for synthetic drugs, especially against numerous diseases (Harjo *et al*., 2004).

In order to produce herbal medicines, standardization for the process of producing herbal extracts or phytochemicals, in which product potency is guaranteed through the consistency of active compound content is essential. The process development and effective analyses are the keys to standardization. Thus, process development in producing valuable natural products is essential to ensure the herbal products met the quality, safety and efficacy requirements.

Drying is known as dehydration process which involves removal of moisture. Most of the drying techniques apply heat on the raw materials which might cause certain level of phytochemical degradation or loss of quality. In particular, phytochemicals that contributes to the beneficial bioactivity of medicinal plants. Thus, the major consideration in herbal drying is to shorten the drying time to preserve the active phytochemicals.

Extraction is referred as a technique to separate active constituents from plant tissue using selected solvents. The extract contains beneficial bioactive compounds of the original plant. Nowadays, there are several of extractions techniques used to increase bioactive compounds from plants such as ultrasound- assisted extraction (UAE), microwave-assisted extraction (MAE), supercritical fluid extraction (SFE) and accelerated solvent extraction (ASE). Among these, ultrasonic assisted extraction (UAE) has been found to enhance extraction efficiency and extraction time. In addition, UAE can be carried out at lower temperature to avoid thermal damage (Rouhani *et al*., 2009; Easmin *et al*., 2014). The improvement of solvent extraction by ultrasound is due to the mechanical effect of acoustic cavitation, which enhances mass transfer and solvent penetration into the plant material by disrupting the cell walls (Vilkhu *et al*., 2008; Rouhani *et al*., 2009). Besides, UAE gave higher productivity, yield and selectivity during extraction of medicinal plant (Easmin *et al*., 2014). Also, better processing time which is reduced time consuming during extraction compared with others conventional method. Low solvent consumption were used and environmental friendly (Easmin *et al*., 2014).

Fractionation is another process to further segregate a complex mixture of crude extract into smaller portions based on solvent property. There are several types of fractionation techniques such as column chromatography and solid phase extraction (SPE). Recently, SPE is widely used for research activity due to the advantages of fast, minimal usage of solvent and wide range selection of solid phase adsorbent (Ku *et al*., 2001).

The kinetic model is a differential equation or empirical equation that describes the independent variables and rate laws for a particular physical, chemical or biological system (Resat *et al*., 2009). The model is a quantitative statement of theory describing the mechanism of a biological or chemical process (Okpokwasili and Nweke, 2005). In the extraction of plant material, kinetic model is used to describe the kinetic profile of a phytochemical compound during extraction process. The mathematical model is very useful in facilitating the optimization, scale- up, simulation of process and controlling the industrial projects by counting the time and energy (San'Ann *et al.,* 2012).

Melastoma malabathricum which is locally known as "senduduk" is a small shrub belonging to the family *Melastomaceae.* This plant is native to tropical and temperate Asia countries, including Malaysia. The promising traditional applications have led to the chemical and biological studies of this plant in modern research. Previous researchers discovered that *M. malabathricum* leaves possessed a number of beneficial bioactivities such as anti-inflammatory, anti-microbial, antiviral, antiparasitic, cytotoxicity, anticoagulant, platelet-activating factor inhibitory, wound healing, antiulcer and antipyretic (Zakaria *et al*., 2012).

In this study, the biological activity was focused on the anti-diabetic activity of the plant crude extract and its fraction. According to Hussein *et al*, (2016), diabetes is a major public health problem in Malaysia, and prevalence of types 2 diabetes has escalated to 20.8% in adult above the age 30. Therefore, intensive studies on *M. malabathricum* are essential, especially its anti-diabetic property due to the presence of quercitrin as the bioactive compound in the leaf extract.

1.2 Problem Statement

Recently, the demand of herbal product is increasing. There are many types of herbal products such as energy drinks, health supplement, as well as herbal tea in the market. The good products commercialized in local market are not sufficient to meet the blooming demand. There is also no standardized procedure in preparing the plant extract according to their applications, for example in herbal medicine, cosmeceutical, and functional foods. *M. malabathricum* leaves are very perishable and therefore always subject to wastage by quick spoilage resulted from dehydration, fungal infection and others (Rajenderan *et al.*, 2010). There are many initiatives taken to solve the problem including drying of leaves, using chemical treatment, manipulation of storage temperature and extracting phytochemicals from leaves. There is lack of research on the processing aspects to produce standardized extracts. The optimization parameters during extraction may help in increasing extracted active compound. Based on previous study of other plants, ultrasonic assisted extraction a great supremacy of extracting phytochemicals in a short period of time (Vilkhu *et al*., 2008). Since the extraction of phytochemicals increased, the biological activity was contributed greatly by the presence of active compounds will most like to increases as well (Joana Gil-Chavez *et al*., 2013). Thus, this research studied on ultrasonic assisted extraction (UAE) method by controlling the condition of extraction in order to produce the maximum quantity of extract.

Quercitrin is one of the quercertin derivatives belonging to a glycosylated flavonoid. It presents as a major compound in *M. malabathricum* leaves. To our knowledge, there has no kinetic study on quercitrin extraction from *M. malabathricum* leaves using ultrasonic assisted extraction. This study was to investigate the kinetic of quercitrin extraction. Then, fractionation process was carried out to further increase the content of quercitrin from the crude extract. This study was also focused on the fractionation using solid phase extraction with strata C_{18} as absorbent to concentrate quercitrin content from the crude extract.

Scientific findings indicated that bioactive fraction from this plant has multiple beneficial effects on biological activities. Hence, *in silico* and *in vitro* studies were performed to determine its anti-diabetic activity. Previously, there is limited study on the effect of quercitrin for anti-diabetic activity using molecular docking simulation. Most of the studies were focused on crude extract, but seldom using quercitrin rich fraction.

1.3 Objectives

The objective of this study were

1. To optimize the drying process for *Melastoma malabathricum* leaves based on high quality of crude extract in quercitrin content, total phenolic content, total flavonoid content and antioxidant activity.
2. To optimize the extraction parameters for high yield of crude extract and quercitrin content using ultrasonic assisted extraction.
3. To optimize the fractionation variables to increase quercitrin content from crude extract using solid phase extraction.
4. To determine the anti-diabetic property of crude extract and its quercitrin rich fraction.

1.4 Scope of Research

The following scopes have been identified to achieve the objectives.

1. To optimize the drying process of *M. malabathricum* leaves with drying temperature between 40 - 80 ^{o}C for high quality of extract with high yield and quercitrin content.
2. To determine the effects of drying on the quality of *M. malabathricum* leaves based on the total phenolic content (TPC), total flavonoid content (TFC) and antioxidant activity.
3. To investigate the drying kinetics of *M. malabathricum* leaves in order to determine the optimum drying temperature and duration. Thin layer models were used to explain the drying process.
4. To optimize the extraction of *M. malabathricum* leaves using ultrasonic assisted extraction based on the yield of crude extract and quercitrin content. The

optimization was carried out based on three different variables such as solid to solvent ratio, particles size, and amplitude in central composite design.

5. To investigate the kinetic extraction of quercitrin from *M. malabathricum* leaves using mathematical modeling such as equilibrium dependent model and diffusion dependent model.
6. To optimize fractionation based on the most influential process parameters, namely ratio composition of eluent, concentration of extract, and volume of column using central composite design.
7. To characterize the crude extract and its fraction using High Performance Liquid Chromatography (HPLC), Thin Layer Chromatography (TLC), and Fourier Transform Infrared Spectroscopy (FTIR) were also performed.
8. To investigate the *in silico* and *in vitro* studies on anti-diabetic property of the plant crude extract and fraction. *In silico* study was carried out using molecular docking based on virtual screening method. Meanwhile, *in vitro* study was carried out using crude extract and fraction on dipeptidylpeptidase-4 (DPP-IV) inhibitor.

1.5 Significance of Study

The herbal industry which was once backyard industry has grown into business that generates multibillion worth of return annually (Kumari *et al.*, 2011). Good quality products commercialized in local market are not sufficient to meet the blooming demand. The significance of this study is to provide the information about the drying process of the herbal plant and optimize the process condition of ultrasonic assisted extraction (UAE) and fractionation using solid phase extraction (SLE) from *M. malabathrcium* leaves. This information can contribute to the other researchers and industry for further study on this plant.

Drying is known as dehydration process which involves removal of moisture. Most of the drying techniques apply heat on the raw materials which might cause certain level of degradation or loss of quality. Possibly, the degraded phytochemicals contribute to the beneficial bioactivity of medicinal plants. Thus, the major contribution is to shorten the drying time, while preserving the active quercitrin in the herbal extract.

Extraction is referred as a technique to separate medicinally active component from plant tissues using selective solvent. The extract concentrates target phytochemicals of the original plant. The extraction was an initial step to release the chemical or bioactive compounds from the plant material which is also a part of food and phyto-pharmaceutical technology (Vinatoru, 2001). For the extraction process, different herbal parts will produce different phytochemical content because of plant matrices. Apart from that, factors such as types of solvent, particles size, temperature, extraction time and extraction techniques played a role in the overall extraction process. The optimum parameters can be used for further study of scaling up process in industry.

Then, follow up with the fractionation process to enrich the quercitrin content. The term of fraction usually refers as the process to separate the chemical substances into different chemical groups. The separated components are divided into different fractions according to the solvent polarity. In this study, the solid phase extraction (SPE) technique was used to optimize the fractionation process. This green chemistry technique was equipped with packed sorbent material, particularly either silica-base or organic resin-based sorbent. It is a relatively new and popular technique for the plant fractionation.

The kinetic model of the extraction process can be used to predict the quantity and quality of herbal extract for herbal industry. In this study, the kinetic of quercitrin extraction is critical for the prediction of quercitrin content. Besides, the change of quercitrin content along the extraction process is also essential in herbal product industry, especially for large scale production.

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