UNIVERSITI PUTRA MALAYSIA

DISCRIMINATION OF Curcuma SPECIES AND BIOACTIVITY CORRELATION USING NMR-BASED METABOLOMICS APPROACH AND SYNTHESIS OF CURCUMIN ANALOGS

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By

TAHANI M. AWIN

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

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DEDICATION

This thesis is dedicated to my husband, children and the spirit of my mother and father.

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

DISCRIMINATION OF *Curcuma* SPECIES AND BIOACTIVITY CORRELATION USING NMR-BASED METABOLOMICS APPROACH AND SYNTHESIS OF CURCUMIN ANALOGS

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Chairman : Associate Professor Faridah Abas, PhD
Faculty : Institute of Bioscience

Curcuma have been widely used in traditional medicine in India and Southeast Asia to treat many human ailments including cancer, inflammation and neurodegeneration. However, there is a lack of consistency in the phytochemical profiles and biological activities of the rhizomes of *Curcuma* species such as *C. zedoaria*, *C. xanthorrhiza*, *C. aeruginosa* and *C. mangga*. Therefore, the aim of this study was to investigate the antioxidant, nitric oxide and α-glucosidase inhibitory properties and characterize the metabolites in selected *Curcuma* extracts by ^{1}H-NMR based metabolomics approach. In the first part of the present study, rhizomes from four *Curcuma* species were dried using three different drying methods and extracted with two different ratios of ethanol (50% and 100%). The extracts were compared in terms of total phenolic contents (TPC), free radical scavenging (DPPH), α-glucosidase and nitric oxide inhibition. Absolute ethanol and freeze-drying were selected to process *C. xanthorrhiza* and *C. mangga* samples used in the second part of the study. The metabolite alterations at seven, eight and nine months old of *C. xanthorrhiza* and *C. mangga* were also investigated. Consequently, eight-month-old *C. xanthorrhiza* and nine-month-old *C. mangga* extracts were fractionated using solid phase extraction (SPE) to obtain n-hexane, chloroform, ethyl acetate and methanol fractions. The active fractions were profiled using ^{1}H-NMR and UPLC-DAD-ESIMS/MS analysis. Due to the richness of curcuminoids in *Curcuma* species, the last part of this study was focused on the synthesis of curcumin analogs. This effort was aimed to overcome the major drawbacks associated with poor solubility of curcumin.

The freeze-dried *C. xanthorrhiza* extracted with absolute ethanol had the highest antioxidant and NO inhibitory activities, whereas the *C. mangga* extract with the same treatment showed the highest α-glucosidase inhibitory activity. Additionally, eight-month-old *C. xanthorrhiza* exhibited the highest NO inhibitory activity, with a large quantity of curcuminoids. Nine-month-old *C. mangga* displayed the highest α-glucosidase inhibitory activity, with high amounts of diterpenoids. The ethyl acetate fraction from *C. xanthorrhiza* and *C. mangga* displayed the most significant bioactivities. Six curcuminoids were identified from *C. xanthorrhiza* and eleven compounds, including curcuminoids and diterpenoids, were identified from *C. mangga.* Fourteen curcumin analogs were synthesized and evaluated for their biological activity. Compounds **2, 6, 8** and **9** showed inhibitory activity against NO, with IC_{50} values ranging from 17 to 21 μM, and four compounds (**1**, **7**, **13** and **14**) demonstrated α-glucosidase inhibitory activity, with IC_{50} values ranging from 19 to 24 μM. A structure-activity relationship (SAR) study revealed that the existence of a hydroxyl substituent and a bromine group in the aromatic rings are crucial for anti-inflammatory and α-glucosidase inhibitory activities.

In conclusion, a ^{1}H-NMR-based metabolomics approach is an excellent tool that can be used to monitor the quality of *Curcuma* species. To the best of our knowledge, this is the first study reporting on the untargeted metabolite profiling of *Curcuma* species using metabolomics approach. This study may support the development of *Curcuma* as an ingredient in medicinal preparations and as a source of food with potential in the development of nutraceutical products.

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

PEMBEZAAN SPESIES *Curcuma* DAN KORELASI BIOAKTIVITI MENGGUNAKAN PENDEKATAN METABOLOMIK BERASASKAN NMR DAN SINTESIS TERBITAN KURKUMIN

Oleh

TAHANI M. AWIN

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Curcuma telah digunakan secara meluas dalam perubatan tradisional di India dan Asia Tenggara untuk merawat pelbagai penyakit manusia termasuk kanser, keradangan dan neurodegeneration. Walau bagaimanapun, terdapat kekurangan konsistensi profil fitokimia dan aktiviti biologi bagi rizom spesies *Curcuma* seperti *C. zedoaria*, *C. xanthorrhiza*, *C. aeruginosa* dan *C. mangga*. Oleh itu, matlamat kajian ini adalah untuk mengkaji aktiviti antioksidan, aktiviti perencatan nitrik oksida dan α-glucosidase dan mencirikan metabolit dalam ekstrak *Curcuma* yang dipilih dengan pendekatan metabolomik berasaskan ^{1}H-NMR. Pada bahagian pertama kajian ini, rizom dari empat spesies *Curcuma* telah dikeringkan menggunakan tiga kaedah pengeringan yang berbeza dan diekstrak dengan dua nisbah etanol (50% dan 100%). Ekstrak dibandingkan untuk jumlah kandungan fenoliknya (TPC), dan bioaktiviti termasuk pemerangkapan radikal bebas (DPPH), perencatan α-glukosidase dan nitrik oksida (NO). Etanol mutlak dan pengeringan sejuk beku digunakan untuk penyediaan sampel *C. xanthorrhiza* dan *C. mangga* yang digunakan dalam bahagian kedua kajian. Perubahan metabolit pada tujuh, lapan dan sembilan bulan juga disiasat. Setelah itu, ekstrak *C. xanthorrhiza* yang berusia lapan bulan dan *C. mangga* berusia sembilan bulan difraksinasi menggunakan ekstraksi fasa pepejal (SPE) untuk mendapatkan pecahan heksana, kloroform, etil asetat dan metanol. Fraksi aktif diprofilkan menggunakan analisis ^{1}H-NMR dan UPLC-DAD-ESIMS/MS. Oleh kerana *Curcuma* kaya dengan kurkuminoid, bahagian terakhir kajian ini memberi tumpuan kepada sintesis analog kurkumin. Ini adalah untuk mengatasi kekurangan utama yang dikaitkan dengan kelarutan kurkumin yang lemah.

C. xanthorrhiza yang dikering secara sejuk beku dan diekstrak dengan etanol mutlak menunjukkan nilai TPC, antioksidan dan aktiviti perencatan NO tertinggi, manakala

C. mangga dengan kaedah rawatan yang sama menunjukkan aktiviti perencatan α-glukosidase tertinggi. Tambahan pula, *C. xanthorrhiza* yang berusia lapan bulan mempamerkan aktiviti perencatan NO tertinggi dengan jumlah kurkuminoid yang tinggi. *C. mangga* berusia sembilan bulan menunjukkan aktiviti perencatan α-glukosidase tertinggi dengan jumlah diterpenoid yang tinggi. Pecahan etil asetat dari *C. xanthorrhiza* dan C. *mangga* menunjukkan bioaktiviti yang paling penting. Enam kurkuminoid telah dikenal pasti dari *C. xanthorrhiza* dan sebelas sebatian, termasuk kurkuminoid dan diterpenoid, telah dikenal pasti dari *C. mangga*. Empat belas analog kurkumin disintesis dan dinilai untuk aktiviti biologi. Sebatian **2, 6, 8** dan **9** menunjukkan aktiviti perencatan NO dengan nilai nilai IC_{50} antara 17 hingga 21μM, dan empat sebatian (**1, 7, 13** dan **14**) menunjukkan aktiviti perencatan α-glukosidase, dengan nilai IC_{50} antara 19 hingga 24 μM. Kajian hubungan struktur dan aktiviti (SAR) mendedahkan kewujudan pengganti hidroksil dan kumpulan bromin dalam cincin aromatik yang penting untuk aktiviti anti-inflamasi dan aktiviti perencatan α-glukosidase.

Sebagai kesimpulan, pendekatan metabolomik yang berasaskan ^{1}H-NMR adalah kaedah yang sangat baik yang dapat digunakan untuk memantau kualiti spesies *Curcuma*. Dalam pengetahuan terbaik kami, ini adalah laporan kajian pertama mengenai profil metabolit yang tidak ditargetkan untuk spesies *Curcuma* menggunakan pendekatan metabolomik berdasarkan ^{1}H-NMR. Kajian ini boleh menyokong pembangunan *Curcuma* sebagai ramuan dalam penyediaan ubat-ubatan dan sebagai sumber makanan yang berpotensi untuk pengembangan produk nutraseutikal.

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

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^{1}H-NMR	Proton Nuclear Magnetic Resonance Spectroscopy
AA	Antioxidant activity
br	broad
β	Beta
^{13}C	Carbon-13
CC	Column Chromatography
COX-2	Cyclooxygenase-2
d	Doublet
dd	Doublet of doublet
DIMS	Direct infusion mass spectrometry
DMEM	Dulbecco's Modified Eagle's Medium
DPPH	Diphenylpicrylhdrazyl
eNOS	Endothelial nitric oxide synthase
FBS	Fetal bovine serum
g	Gram
GAE	Gallic Acid Equivalent
GC-MS	Gas Chromatography- Mass Spectrometry
HCA	Hierarchical Cluster Analysis
HMBC	Heteronuclear Multiple-bond Correlation
HPLC	High Performance Liquid Chromatography
HSQC	Heteronuclear Single-quantum Correlation
Hz	Hertz
IC_{50}	Inhibition Concentration at 50 percent
IFN-γ	Interferon gamma
iNOS	Inducible nitric oxide synthase
J	Coupling constant in Hz
L	Litre
LC-MS	Liquid Chromatography–Mass Spectrometry
LPS	Lipopolysaccharide
m	Multiplet

m.p.	Melting point
µg	Microliter
µL	Microliter
m/z	Mass per Charge
MeOH	Methanol
MHz	MegaHertz
mL	Milliliter
mm	Millimeter
mol	Molar
MS	Mass Spectrometry
MTT	3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl tetrazolium bromide
MVDA	Multivariate data analysis
ng	Nanogram
nNOS	Neuronal nitric oxide synthase
NO	Nitric oxide
ºC	Degree in Celsius
PLS-DA	Partial Least Squares–Discriminant Analysis
^{1}H	Proton
PC	Principal Component
PCA	Principal Component Analysis
PLS	Partial Least Squares
ppm	Part Per Million
q	Quartet
RAW264.7	Murine monocyte-macrophage cell line
RMSECV	Root Mean Square Error of Cross Validation
RMSEC	Root Mean Square Error of Calibration
RNS	Reactive nitrogen species
ROS	Reactive Oxygen Species
RT	Room temperature
s	Singlet
SIMCA	Soft Independent Modeling of Class Analogy

TLC	Thin Layer Chromatography
TNF-α	Tumor necrosis factor Alpha
TPC	Total Phenolic Contents
UV	Ultraviolet
UV/VIS	Ultravoilet/visible
δ	Chemical Shift in ppm

CHAPTER 1

INTRODUCTION

1.1 Background

Products derived from medicinal plants have been key source of medicines globally for centuries (McChesney et al., 2007). During the 20th century, prior to the "Synthetic Era", approximately 80% of medicines consumed were a natural product from medicinal plants (Singh et al., 2014). Recently, an upsurge in natural product based drug research has been witnessed due to their ubiquity, low cost, improved tolerability, relatively minimal side effects and structural diversity (Singh et al., 2014). There was a projection that nearly 70% of novel chemical bodies utilized in the practice of medicine were acquired from natural products, either directly or indirectly. The importance of traditional medicine has attracted attention from the World Health Organization, which have thus established guidelines, strategies and standards for the usage of medicinal plants (Baker et al., 2007; McChesney et al., 2007; Singh et al., 2014).

In meeting the need for primary health care, the role of medicinal plants cannot be overemphasized, especially in developing countries, due to their low cost, effectiveness, safety and availability (Agra et al., 2007). Likewise, the high costs of prescribed drugs for health maintenance have driven interest in the search for medicinal plants with potential new plant-derived medicines (Hoareau and DaSilva, 1999). Previously, most medicines were obtained from plants, either in a crude form extracted from different parts or by merging these parts as raw extracts (Ayyanar and Ignacimuthu, 2011).

The therapeutic use of plants on the basis of bioactive compounds in drug discovery occurs through four different pathways, described as follows: a) Using complete plants or parts of plants as a herbal therapies, e.g., garlic, echinaceas, *Ginkgo biloba*, and cranberry; b) using isolated active agents for formulating drugs from plants, e.g., morphine, vinblastine, digitoxin, taxol, vincristine, digoxin, and reserpine; c) searching for active agents with novel or established structures and then using them in the semi-synthesis of active compounds for use as registered drugs with greater activity and reduced toxicity, e.g., metformin, nabilone, oxycodone, and taxotere. These agents are subsequently used for chemical, clinical and pharmacological analysis (Fabricant and Farnsworth, 2001).

The different uses of medicinal plants in various global regions are key for creating new guidelines for the dissemination of alternative medicine with greater economic and social benefits. Medicinal plants have played a significant part in overcoming many health challenges in Malaysia. Plant mixtures used for therapeutic purposes have previously been documented (Herbal Medicine Research Centre, 2002; Zaidan et al.,

2005). Well over a hundred Malaysian plant species have been reported to have medicinal potential. Quite a few of these plants are commonly utilized, and their utilization in traditional medicine has continued over many years (Zaidan et al., 2005). In fact, more than 250,000 species of Malaysia's higher plants have been shown to have healing properties, but only 5–15% of them have been studied. Therefore, it is pertinent to find plants containing valuable therapeutic compounds (Chew et al., 2011).

Having originated from the Indo-Malayan parts of Asia, the genus *Curcuma is* comprised of more than 80 species of rhizomatous herbs (Jung et al., 2012) which are widely distributed in the tropical regions of the world including but not limited to Asia, Africa and Australia (Policegoudra et al., 2007; Angel et al., 2012). *Curcuma* species demonstrated intra- and inter-specific variation with respect to biologically active compounds together with morphological differences in regard to the above-ground floral and vegetative characters in addition to the below-ground rhizome features besides curcuminoids and essential oil (Sasikumar, 2005; Jung et al., 2012; Saensouk et al., 2015).

1.2 Problem Statement

Although the traditional Chinese medicine and Indian Ayurvedic system of medicine have long recognized the medicinal potentials of *Curcuma* in crude form, extensive research interests in the bioactivity and pharmacological effect of this genus have been witnessed in the last few decades, particularly the cultivated species (Sasaki et al., 2003; Sasikumar, 2005). The powder derived from rhizomes of *Curcuma* species is widely used as food preservative, coloring material, spice and household remedy for sinusitis, biliary, hepatic disorders, diabetic wounds, anorexia and rheumatism in China, South-East Asia and India (Sasaki et al., 2003; Ahmed Hamdi et al., 2014). Despite having such wide spectrum of biological activities, the antioxidant, nitric oxide (NO) and α-glucosidase inhibitory activities of *C. zedoaria*, *C. xanthorrhiza*, *C. aeruginosa* and *C. mangga* was not reported till date.

Meanwhile, the increase in public demand for natural medicines has resulted in increased commercial activity and production of these medicines. This has led to a growing concern with regard to ensuring the quality and safety of medicinal plants and herbal drugs. For example, the use of *Curcuma* species in many traditional preparations in Malaysia lead to issues with the quality of the raw materials, the effect of processing, the content of the metabolites and the efficacy of the final products. To effectively coordinate the quality, it has become essential to develop reliable and sensitive quality-control methods using an NMR metabolomics approach.

Furthermore, medicinal chemistry, which incorporates the fields of pharmacology and chemistry, is said to be one of the fastest growing fields in the scientific disciplines. Designing and finding novel pharmaceutical medicines from natural and synthetic

products using different pharmacological assays is the key aim of medicinal chemistry. The purification of active compounds from therapeutic plants was the main target in the early stages of medicinal chemistry, while less attention was given to the synthesis of natural products; meanwhile, finding new therapeutic drugs relied solely on slow and careful chances (Gualtieri, 2000). However, after several years of progress, the synthetic chemistry has gradually become recognized as the best means of isolating natural products for advancing medicinal chemistry because of its exceptional efficacy.

1.3 Objectives

This study was designed to provide a solution to numerous problems and could lead to platforms for obtaining valuable extracts for treating numerous diseases. The main objective of this research was to profile and characterize the bioactive metabolites in *C. zedoaria*, *C. xanthorrhiza*, *C. aeruginosa* and *C. mangga* using ^{1}H-NMR-based metabolomics and to synthesize curcumin analogs. For the realization of this aim, several specific objectives were proposed. Firstly, the effect of different solvents and drying methods on the anti-inflammatory, antioxidant and α-glucosidase inhibitory activities of four *Curcuma* species was evaluated. The most active solvent extracts and their drying methods were chosen for comparison, and the phytochemical content of selected *Curcuma* species at different developmental stages was also evaluated. Proton NMR spectroscopy was used to quantify the metabolites, and the most active species was selected and fractionated with different solvent polarity. The chemical constituent profile of the most desirable and potent extract was correlated with their biological activities. Finally, synthetic curcumin analogs and their biological activities were also evaluated. The results will contribute immensely to the existing literature and perhaps shade more light on pharmacological study of *Curcuma* species.

The specific objectives of this study were as follows:

1. To determine the effect of different drying methods and ethanol ratio on antioxidant, α-glucosidase and nitric oxide inhibitory activities of four selected *Curcuma* species and its phytochemical constituents using ^{1}H-NMR based metabolomics.
2. To evaluate the effects of growth stages (seven, eight and nine months) on the metabolites of the most active *Curcuma* species using ^{1}H-NMR based metabolomics.
3. To profile the different polarity fractions of *Curcuma xanthorrhiza* and correlate the chemical profile with nitric oxide inhibitory activity.
4. To profile the different polarity fractions of *Curcuma mangga* and correlate the chemical profile with α-glucosidase inhibitory activity.
5. To synthesize curcumin analogs and develop the structure activity relationships (SAR).

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