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CHEMICAL PROFILE AND ANTI-DIABETIC ACTIVITY OF Ipomoea aquatica Forssk. EXTRACT ELUCIDATED BY NMR-BASED METABOLOMICS

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

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Chairman : Assoc. Prof. Faridah Abas, PhD
Institute : Bioscience

Diabetes mellitus (DM) is one of non-communicable disease (NCDs) that is characterized by high glucose content in blood or hyperglycemia, which can lead to long term complications and even death in the case of no proper treatment performed. Therefore, effective control of blood sugar has been known to be one the main issue in dealing with DM and its associated complications. In this study, the influence of various ethanol ratios (0, 20, 50, 80, and 100%) as an extraction solvent and different drying methods including air drying (AD), sun drying (SD) and oven drying (OD) on phytochemical constituents of *I. aquatica* were investigated using a proton nuclear magnetic resonance (^{1}H NMR) based metabolomics approach. The highest α-glucosidase inhibitory activity was observed for absolute ethanol extract from the OD method with an IC_{50} value of 204.0 ± 59.0 µg/mL and TPC value of 22.0 ± 0.7 µg GAE/mg extract. Correlation between the α-glucosidase inhibitory activity and the metabolite were analyzed using a partial least square (PLS) analysis. The metabolites that might be responsible for the activity were quercetin derivatives, chlorogenic acid derivatives, sucrose and fructose.

Along with our *in vitro* study, the ^{1}H NMR based metabolomics also been applied to the *in vivo* model (Sprague-Dawley rats). The *in vivo* model was first evaluated for understanding the metabolic link between the obesity (OB), lean diabetic (ND+STZ) and obese diabetic (OB+STZ). In this model, the OB+STZ rats mimics the symptom in the type 2 diabetes (T2DM), whereas the lean diabetic rats (ND+STZ) mimics type 1 diabetes (T1DM). The results of multivariate data analysis (MVDA) managed to highlight several similarities and dissimilarities in metabolites level in OB, ND+STZ and OB+STZ. This finding indicates both of the diabetic group (ND+STZ and OB+STZ) and OB rats shared some similar features especially in metabolic traits (2-oxoglutarate, succinate, tryptophan (TRP) and dimethylamine (DMA)), where it manage to highlights the importance of tricarboxylic acid cycle (TCA) and tryptophan (TRP) metabolism in diabetes progression. On the other hand, the differences between

ND+STZ and OB+STZ can be seen in the synthesis of ketone bodies and branched chain amino acid (BCAA).

Additionally, the effectiveness of the *I. aquatica* (IA) extracts as a hypoglycemic agent was also tested *in vivo* using obese Sprague-Dawley streptozotocin (STZ) -induced rats (OB+STZ). The rats were treated for 1 month, and the pathophysiological changes in serum and urine of these treated rats (OB+STZ+IA) and non-treated obese-diabetic rats (OB+STZ) were compared. The serum was assessed for biochemical parameter while the urine was evaluated using ^{1}H NMR. The result from serum showed there was no significant difference ($p > 0.05$) between the serum glucose of OB+STZ+IA (20.32 ± 8.79 mmol/L) and OB+STZ (24.60 ± 1.67 mmol/L) due to huge variation between the individuals. Interestingly, we found that there was clear discrimination between the urine spectra of OB+STZ+IA and OB+STZ by using ^{1}H-NMR metabolomic approach. The differences between the biochemical results from serum as compared to urine are probably due to the sensitivity of the instruments and the nature of the sample. Analysis of altered metabolites reveals that administration of *I. aquatica* extracts affects TCA cycle, creatine and creatinine metabolism, amino acids metabolism and nicotine and nicotinamide metabolism. This study highlights the basis for future investigations of *I. aquatica* as a source of food that has the potential for nutraceutical enhancement and as an ingredient in medicinal preparation.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Master Sains

PROFIL KIMIA DAN AKTIVITI ANTI-DIABETIK EKSTRAK *Ipomoea aquatica* Forssk. DIJELASKAN OLEH METABOLOMIK BERASASKAN NMR

By

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September 2016

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Kencing manis (DM) merupakan salah satu penyakit tidak berjangkit (NCD) yang dicirikan oleh kandungan gula yang tinggi dalam darah atau hiperglisemia, di mana ia boleh membawa kepada komplikasi jangka panjang dan kematian jika tidak dirawat dengan sebaiknya. Justeru, keberkesanan mengawal gula dalam darah telah dikenalpasti sebagai salah satu isu utama di dalam menangani DM dan kompilaksi yang berkaitan dengannya. Di dalam kajian ini, pengaruh nisbah etanol (0, 20, 50, 80, and 100%) sebagai pelarut pengekstrakan dan teknik pengeringan yang berbeza termasuk pengeringan udara (AD), pengeringan matahari (SD) and pengeringan ketuhar (OD) ke atas sebatian fitokimia *Ipomoea aquatica* dikaji menggunakan pendekatan metabolomik berasaskan proton resonans magnet nukleus (^{1}H NMR). Perencatan aktiviti α-glukosidase yang tertinggi didapati pada ekstrak 100% etanol daripada pengeringan OD dengan nilai IC_{50} 204.0 ± 59.0 µg/mL dan jumlah kandungan fenolik (TPC), 22.0 ± 0.7 µg GAE/mg ekstrak. Korelasi di antara perencatan aktiviti α-glukosidase dan metabolit telah dianalisa menggunakan analisis kuasa dua terkecil separa (PLS). Metabolit yang mungkin mempengaruhi aktiviti tersebut adalah terbitan kuasertin, terbitan asid klorogenik, sukrosa dan fruktosa.

Di samping kajian *in vitro*, pendekatan metabolomik berasaskan ^{1}H-NMR juga dijalankan ke atas model *in vivo* menggunakan tikus *Sprague Dawley*. Tujuan utama model *in vivo* ini adalah untuk memahami hubungan diantara obesiti (OB), bukan-obes diabetes (ND+STZ) dan obes diabetes (OB+STZ) dalam mengenal pasti jenis diabetes di alami oleh tikus streptozotocin (STZ) teraruh. Dalam model ini, tikus OB+STZ mengalami gejala atau simptom yang meyamai diabetes jenis kedua (T2DM), manakala tikus dari ND+STZ menyerupai diabetes jenis pertama (T1DM). Keputusan daripada analisis multivariat (MVDA) berjaya menemukan beberapa persamaan dan perbezaan pada kandungan metabolit tikus OB, ND+STZ dan OB+STZ. Penemuan ini menandakan kedua-dua kumpulan diabetes (ND+STZ dan OB+STZ) dan tikus OB berkongsi ciri-ciri khususnya di dalam trait metabolit (2-oksoglutarat, suksinat, triptofan (TRP) dan dimetilamina (DMA)), di mana ia berjaya menunjukkan

kepentingan dalam kitaran trikarbosilik asid (TCA) dan metabolisma TRP di dalam patogenesis diabetes. Di samping itu, perbezaan di antara ND+STZ dan OB+STZ boleh didapati pada jasad keton dan sintesis asid amino bercabang (BCAA).

Di samping itu, keberkesanan ekstrak *I. aquatica* (IA) sebagai agen hipoglisemik juga di kaji melalui kajian *in vivo* menggunakan tikus OB+STZ. Tikus-tikus ini telah dirawat selama 1 bulan, dan perubahan patofisiologi di dalam serum dan urin (air kencing) tikus yang dirawat (OB+STZ+IA) dan tikus yang tidak dirawat (OB+STZ) dibandingkan. Serum dianalisis untuk parameter biokimia, manakala urin dinilai menggunakan ^{1}H-NMR. Keputusan serum menunjukan tiada perubahan signifikan di antara serum glukosa tikus daripada kumpulan OB+STZ+IA (20.32 ± 9.49 mmol/L) dan OB+STZ (24.60 ± 1.67 mmol/L) kerana terdapat variasi yang besar di antara tikus-tikus di dalam kumpulan yang sama. Walaubagaimanapun, terdapat perbezaan di antara OB+STZ dan OB+STZ+IA melalui spektrum urin menggunakan metabolomik berasaskan ^{1}H-NMR. Perbezaan keputusan biokimia di antara serum dan urin mungkin disebabkan sensitivi instrumen dan sifat semulajadi sampel. Analisis menunjukan *I. aquatica* berjaya merubah metabolisma seperti kitaran TCA, kreatin dan kreatinine, asid amino dan nikotin dan nikotinamida. Kajian ini berjaya menekankan potensi *I. aquatica* sebagai sumber makanan nutraseutikal yang berpotensi dan juga sebagai bahan dalam pemyediaan ubat-ubatan.

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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 of Master of Science. The members of Supervisory Committee are as follows:

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LIST OF ABBREVIATIONS

^{1}H	Proton
3-HAA	3-hyroxyanthranilic
3-HB	3-hydroxybutyrate
ACUC	Animal Care and Use Committee
AD	Air dry
ATP	Adenosine triphosphate
BCAA	Branched chain amino acid
br	Broad
CMC	Carboxymethyl cellulose
CPMG	Carr-Purcell-Meiboom-Gill
d	Doublet
dd	Doublet of doublet
DM	Diabetes mellitus
DMA	Dimethylamine
DMG	Dimethylglycine
EGP	Endogenous glucose production
ER	Endoplasmic reticulum
GAD_{65}	Glutanic acid decarboxylase
HCA	Hierarchical cluster analysis
Hfd	High fat diet
HLA	Human leukocyte antigen
HMBC	Heteronuclear multiple bond correlation
IA	*Ipomoea aquatica*
IAA	Insulin autoantibodies
ICA	Islet cell autoantibodies
IDDM	Insulin dependent diabetes mellitus
J	Coupling constant in Hz
KK	Kuo kondo mouse
KYN	Kynurenine
LADA	Latent autoimmune diabetes
LDH	Lactate dehydrogenase
m	Multiplet
MHz	Megahertz
MNA	1-Methylnicotinamide
MOH	Ministry of Health Malaysia
mRNA	Messenger ribonucleic acid
MSG	Monosodium glutamate
NAD	Nicotinamide
Nd	Normal diet
ND	Normal/Lean
ND+STZ	Lean diabetic
ND+STZ+MET	Lean diabetic treated with metformin
NDDM	Insulin dependent diabetes mellitus
NMR	Nuclear magnetic resonance
NZO	New Zealand obese mouse
OB	Obese
OB+STZ	Obese diabetic
OB+STZ+IA	Obese diabetic treated with *I. aquatica* extract
OB+STZ+MET	Obese diabetic treated with metformin

OD	Oven dry
OGTT	Oral glucose tolerance test
OPLS-DA	Orthagonal partial least square
PC	Pyruvate complex
PCA	Principle component analysis
PDC	Pyruvate dehydrogenase complex
PLS	Partial least square
PLS-DA	Partial least square discriminant analysis
QA	Quinolinic acid
RBC	Red blood cell
s	Singlet
SD	Sun dry
STZ	Streptozotocin
t	Triplet
T1DM	Type 1 diabetes
T2DM	Type 2 diabetes
TCA	Tricarboxylic acid
TPC	Total phenolic content
TRP	Tryptophan
TSP	Trimethylsilyl propionic acid sodium salt
VIP	Variable importance in the projection
WHO	World Health Organization
δ	Chemical shift in ppm

CHAPTER 1

INTRODUCTION

1.1 Background

Diabetes mellitus (DM) is one of the major degenerative diseases that haunt major populations in this world today (Van den Driessche et al., 2009). It is usually associated with other diseases such as hypertension, atherosclerosis, and microcirculatory disorders (Milicevic et al., 2008; Moore et al., 2009). It can also cause long-term complications such as retinopathy, nephropathy, neuropathy and angiopathy (Nicolucci et al., 1996). In Malaysia, the prevalence of adults with DM is nearly 1.5 million, and this disease increased by 3.3% over the last few decades (Azimah et al., 2009).

DM can essentially be divided into two main groups, Type 1 and Type 2, based on the requirement for insulin. Type 1 is insulin-dependent diabetes mellitus, while Type 2 is non-insulin dependent. Approximately 90% of DM cases worldwide are Type 2 diabetes (Alberti & Zimmet, 1998), characterized by a combination of defects in insulin secretion and insulin sensitivity. Type 2 DM is usually linked with another disease such as obesity (Grundy, 2004; Parton et al., 2007; Pradhan, 2007) and cardiovascular (Desouza et al., 2003; Wright & Frier, 2008) disease, associated with glucose metabolism deregulations. All these factors make Type 2 DM a complex disease that is difficult to understand (Leahy, 2005; McIntyre & Walker, 2002).

One of the ways to manage DM is by controlling the glycemic/glucose level in the blood. Previous studies have confirmed that the effective control of the blood glucose level in DM can significantly reduce the risk of developing diabetes complications (Ohkubo et al., 1995; UKPDS, 1998). The search for effective and safer anti-hyperglycemic drugs is increasing as the current insulin therapy and oral hypoglycemic agents contain side effects that are harmful to health (Holman & Turner, 1991). To overcome this matter, alternative medicine sources such as plants are used in treating DM. From the literature, there are more than 800 plant species traditionally used as anti-hyperglycemic agents (Harbilas et al., 2009). These include fruits and vegetables that are known to contain high levels of vitamins and phytochemicals that are beneficial to humans (Franceschi et al., 1998).

Fruits and vegetables such as *Momordica charantia* (bitter melon), *Coriandrum sativum* (coriander), *Brassica juncea* (leaf mustard) and *Ipomoea batatas* (sweet potato) have been tested for their hypoglycemic activities using animal models, and all showed promising results (Day et al., 1990; Khan et al., 1995; Kusano & Abe, 2000; Swanston et al., 1990). Previously, an infusion and diet containing *Coriandrum sativum* was shown to reduce hyperglycemia during the development of streptozotocin (STZ) - induced diabetes in mice (Swanston et al., 1990). *Ipomoea batatas* L. (sweet potato) produced a significant reduction in the glucose levels of Zucker fatty rats after the third week of treatment, and this result is comparable to a standard anti-diabetic drug,

troglitazone (Kusano & Abe, 2000). However, the search to find more plant extracts that can be scientifically proven to contain hypoglycemic activities is still ongoing. Demands for the use of these plants are increasing due to their low cost, easy availability and low side effects (Harbilas et al., 2009).

In the present study, *Ipomoea aquatica* or locally known as "kangkung" has been chosen as the potential plant to treat obese rats with induced diabetes. *I. aquatica* is a green leafy vegetable, a semi-aquatic plant that belongs to the Convolvulaceae family. It is easily grown and has been cultivated throughout Southeast Asia and consumed as a vegetable (Meira et al., 2012). Chen and Chen (1992) reported that among the vegetables, *I. aquatica* is one that is rich in carotenoids and chlorophylls. Based on a previous study conducted by Hamid et al. (2011), there is a significant difference ($p < 0.001$) in the hypoglycemic activity of *I. aquatica* extracts at 200 mg/kg compared to the control of Swiss albino mice. Malalavidhane et al. (2001) also reported that the hypoglycemic activity of *I. aquatica* is on par with the standard anti-diabetic drug, tobultamide. However, the mechanism of this plant in diabetes is yet unknown.

An animal model was used in this study to mimic human DM. Streptozotocin (STZ) is a broad spectrum antibiotic and a powerful alkylating agent that was injected into the rats, resulting in the destruction of insulin-producing β-cells (Bolzán & Bianchi, 2002). A previous study (Nieman et al., 2006) found that a diabetic state changes metabolites such as the methyl group, choline, and homocysteine compared to the control. Due to the complexity of the disease, Zhang et al. (2008) suggested that a metabolomics approach should be used in conducting diabetes research. Metabolomics studies can be defined as an attempt to measure all the metabolites that are present in a cell, tissue or organism due to genetic modification or physiological stimulus (Bino et al., 2004; Nicholson et al., 2005; Nicholson et al., 1999; Oliver, 2006; Oliver et al., 1998).

Metabolomics studies use biofluids or cell or tissue extracts to collect metabolic data. These metabolic data are important for the identification of sensitive and specific traits of metabolic disorders, and this information is crucial, especially for early-stage detection and evaluation of therapy in treating DM (Sebedio et al., 2009). In addition, biofluids from animal and human studies are usually relatively easy to obtain high in volume and produce a consistent result (Sebedio et al., 2009). In general, the most common technologies that have been used in metabolomics studies are NMR, LC-MS, GC-MS and HPLC. Compared to the others, NMR-based metabolomics is preferred due to its robustness, reproducibility and non-destructive nature (Nicholson et al., 2002).

1.2 Problem statements

The effect of the extraction solvent on plant phytochemicals may offer much information on the extraction efficiency to maximize the benefit of plants as medicine or food ingredients. However, little information has been reported on the effects of solvent ratios on *I. aquatica* bioactive compounds, and although extensive studies have been performed on this plant as an anti-diabetic agent (Hamid et al., 2011;

Malalavidhane et al., 2001; Malalavidhane et al., 2000), little is known regarding chemical analyses that can describe the metabolic alterations resulting from phytochemical intervention in diabetic-induced animal models.

1.3 Objectives

Therefore, the present study was conducted to evaluate the anti-diabetic activity of *I. aquatica* extract by using metabolomics approach. This approach will allow better understanding in terms of the mechanism of action and also help to identify chemical and biomarkers associated with anti-diabetic and *I. aquatica* treatment. Hence, the objectives of this study were:

1. To evaluate the effect of drying methods and solvent ratio on phytochemicals constituents and α-glucosidase inhibitory activity of *I. aquatica* using ^{1}H NMR based metabolomics.
2. To identify metabolite variation in lean and obese streptozotocin (STZ)-induced diabetic rats.
3. To determine the bio-markers relating to the anti-diabetic effect of *I. aquatica* extracts in streptozotocin (STZ)-induced diabetic rats via ^{1}H NMR-based metabolomics approach.

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LIST OF PUBLICATIONS

Azliana Abu Bakar Sajak, Faridah Abas, Amin Ismail & Alfi Khatib (2016). Effect of Different Drying Treatments and Solvent Ratios on Phytochemical Constituents of *Ipomoea aquatica* and Correlation with α-Glucosidase Inhibitory Activity. *International Journal of Food Properties, 19*, 2817-2831.

Azliana Abu Bakar Sajak, Ahmed Mediani, Maulidiani, Faridah Abas, Amin Ismail and Alfi Khatib. Metabolite Variation in Lean and Obese Streptozotocin (STZ)-Induced Diabetic Rats via ^{1}H NMR-Based Metabolomics Approach. *Applied Biochemistry and Biotechnology*. DOI: 10.1007/s12010-016-2352-9.

Azliana Abu Bakar Sajak, Ahmed Mediani, Maulidiani, Faridah Abas, Amin Ismail and Alfi Khatib. Intervention of *I. aquatica* Extract on Streptozotocin (STZ)-Induced Diabetic Rats via ^{1}H NMR-Based Metabolomics Approach. Submitted to Phytomedicine.

CONFERENCE

Azliana Abu Bakar Sajak, Faridah Abas, Amin Ismail & Alfi Khatib. Application of ^{1}H-NMR Based Metabolomics for Determination of Biological Activity in *Ipomoea aquatica* Extracts Prepared by Different Drying Method and Solvent Ratio. International Conference of Natural Product 2014, Putrajaya, Malaysia, 18-19 March 2014 (Poster presenter).

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