UNIVERSITI PUTRA MALAYSIA

METABOLIC CHANGES ASSOCIATED WITH THE EFFECT OF Morinda citrifolia L. LEAF EXTRACT IN THE PREVENTION AND TREATMENT OF OBESITY IN SPRAGUE- DAWLEY RATS

NAJLA GOODA SAHIB

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By

NAJLA GOODA SAHIB

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

August 2014

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DEDICATIONS

I dedicate this thesis to:

*First and foremost, my parents**, Khatijah and Abdool Rassid Gooda Sahib**, for having always believed in me and prayed for me*

*My sister, **Nuzhah,** who has always been here to listen to my PhD troubles and whose advice always makes sense*

*My brothers **Irfaan** and **Isfaaq** who always make me feel good about my cooking*

*My friends, **Fazilah and Maryam***

*My labmates, **Hafeedza, Asraf and Ahmed***

*My ibu away from home, **Dr Ezra Jamal**, for the good food and the love*

*My in-laws, **Osman, Zabeen, Amal, Hishaam and Nadjmah Jambocus** for being so understanding*

*My husband, my better half, the coolness of my eyes, **Adnaan Zayd Jambocus**, thank you for your ultimate support, belief, love and most importantly for the amazing calmness you bring to my crazy life ...I love you for the sake of Allah*

*And finally, the little ray of hope and life, **Ubayd Ibn Zayd,** who managed to grow inside me, despite all the stress, I am sorry for putting you through the pains of PhD thesis writing, way before you were born, but I promise to love you forever…*

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

METABOLIC CHANGES ASSOCIATED WITH THE EFFECT OF *Morinda citrifolia* L. LEAF EXTRACT IN THE PREVENTION AND TREATMENT OF OBESITY IN SPRAGUE- DAWLEY RATS

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August 2014

Chair: Prof. Azizah Abdul Hamid, PhD

Faculty: Food Science and Technology

The prevalence of obesity is increasing worldwide, both in developed and developing nations and a high fat diet is one of the main factors. It is known that obesity also increase the predisposition to other diseases such as diabetes and cardiovascular diseases through the involvement of various metabolic pathways. The lack of anti-obesity drugs and the popularity of alternative and complementary medicine has encouraged research in finding phytochemical strategies to this multifaceted disease. In this study, extracts of *Morinda citrifolia* leaf of different maturity and extracted with different ethanol concentrations were assessed for their bioactivity (total phenolic content, DPPH scavenging activity, inhibitory effects on pancreatic and lipoprotein lipase activity) as potential anti-obesity agents. Mature leaves extracted with 60% ethanol, labeled as MLE 60 had the highest lipase inhibitory effect and was further analysed for its bioactive content using ^{1}H Nuclear Magnetic Resonance spectroscopy (^{1}H NMR), Liquid Chromatography Mass Spectroscopy (LCMS) and High Performance Liquid Chromatography (HPLC). MLE 60 was found to contain flavonoids, including catechin, kaempherol and rutin. The anti-obesity effect of the same extract was subsequently assessed for the prevention and treatment of obesity, *in vivo*. In the preventive study, lean Sprague- Dawley rats were fed a high fat diet (HFD) with or without MLE 60 for 12 weeks and assessed for weight gain, adiposity, appetite, fecal fat excretion and plasma biochemistry. Supplementation of MLE 60 in the HFD group prevented weight gain (98.6-129.6%) as compared to the control HFD only group (176.3%), reduced adiposity (3.45-4.04%) as compared to the control obese group (6.98%), increased fecal fat excretion (11.39-19.58%) compared to 5.34% for the control group, without any effect on appetite. The plasma biochemistry profiles were improved, with a marked decrease in total triglycerides, leptin and insulin levels. For the treatment study, HFD induced obese Sprague- Dawley rats were treated with MLE 60 post feeding with a HFD for 12 weeks. Similar parameters as the preventive study were measured. After 9 weeks

of treatment, no significant weight loss was achieved in any of the treated group, including the group treated with the standard control drug Orlistat®, though positive effects were observed on adiposity, fecal fat content, plasma lipids, insulin and leptin levels. The inducement of obesity and treatment with MLE 60 on metabolic alterations were then further elucidated using a ^{1}H NMR based metabolomics approach, where the urine and serum of obese and lean rats were compared for biomarkers associated with HFD induced obesity. Multivariate analysis, including the projections to latent structures-discriminant analysis (OPLS-DA) was used for biomarkers identification. Discriminating metabolites involved were products of various metabolic pathways, including glucose metabolism and TCA cycle (lactate, 2-Oxoglutarate, citrate, succinate, pyruvate, acetate), amino acid metabolism (alanine, 2-hydroxybutyrate), choline metabolism (betaine), creatinine metabolism (creatinine) and gut microbiome metabolism (hippurate, phenylacetylglycine, dimethylamine, trigonelline). Treatment with MLE 60, specifically at 250 mg/kg, resulted in significant improvement in the metabolic perturbations caused by HFD induced obesity as demonstrated by the proximity of the treated group to the normal group in the OPLS-DA score plot and the change in trajectory movement of the diseased group towards the healthy group upon treatment. A relative quantification of discriminating metabolites showed improvements in the treated groups. This study reports on the potential anti-obesity effect of MLE 60, based on its lipase inhibiting ability as reflected as by the increase fecal fat content and its positive effect on pro obesity factors including leptin and insulin. It also confirms that consumption of a HFD caused metabolic perturbations other than traditionally studied parameters, which can be improved by the supplementation of plant extracts like MLE 60 and ^{1}H NMR based metabolomics can be a good tool in obesity research.

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

PERUBAHAN METABOLIK BERKAITAN DENGAN KESAN DAUN *Morinda Citrifolia* L. DI DALAM RAWATAN PENCEGAHAN DAN PEMULIHAN OBESITI TERHADAP TIKUS SPRAGUE- DAWLEY

Oleh

NAJLA GOODA SAHIB

Ogos 2014

Pengerusi: Prof. Azizah Abdul Hamid, PhD

Fakulti: Sains dan Teknologi Makanan

Kadar obesiti semakin meningkat di seluruh dunia sama ada di negara maju ataupun di negara membangun dan diet yang berlemak tinggi adalah salah satu faktor utama kepada masalah ini. Obesiti juga cenderung untuk meningkatkan risiko penyakit-penyakit lain seperti kencing manis dan penyakit kardiovaskular yang melibatkan pelbagai laluan metabolik. Kekurangan ubat anti -obesiti dan populariti perubatan alternative dan tradisional telah menggalakkan penyelidikan dalam mencari strategi fitokimia yang berkesan kepada penyakit ini. Dalam kajian ini, daun *Morinda citrifolia* yang telah diekstrak dengan larutan yang berbeza dinilai aktiviti biologinya (kandungan jumlah fenol, aktiviti penghapusan DPPH, kesan rencatan terhadap aktiviti pankreas dan lipoprotein lipase) sebagai agen anti-obesiti yang berpotensi. Daun matang yang telah diekstrak dengan 60% etanol, yang dilabel sebagai MLE 60 mempunyai kesan perencatan terhadap lipase yang paling tinggi dan kemudiannya telah dianalisis kandungan bioaktifnya dengan menggunakan 1H Nuklear Magnetic Resonance spektroskopi (1H NMR), Liquid Chromatography Mass Spectroscopy (LCMS) dan Kromatografi Cecair Prestasi Tinggi (HPLC). MLE 60 telah didapati mengandungi flavonoid, termasuk catechin, kaempherol dan rutin. Ekstrak yang sama kemudiannya telah dinilai keberkesanannya untuk pencegahan dan pemulihan obesiti secara *in vivo*. Dalam kajian pencegahan, tikus Sprague Dawley telah diberi makan diet berlemak tinggi (HFD) dengan atau tanpa MLE 60 selama 12 minggu dan telah dinilai berat badan, adiposity, selera makan, perkumuhan lemak di dalam tinja dan bahan biokimia di dalam plasma. Kumpulan HFD yang diberi suplemen MLE 60 telah menunjukkan kadar pertambahan berat badan yang rendah (98.6-129.6%) berbanding dengan kumpulan kawalan HFD (176.3%), adiposity yang rendah (3.45- 4.04%) berbanding dengan

kumpulan kawalan HFD (6.98 %), perkumuhan lemak di dalam tinja yang tinggi (11. 39 -19.58%) berbanding dengan 5.34% bagi kumpulan kawalan, tanpa apa-apa kesan ke atas selera makan. Profil biokimia plasma telah bertambah baik dengan penurunan yang ketara dalam jumlah trigliserida, leptin dan tahap insulin. Untuk kajian pemulihan terhadap obesiti, tikus Sprague - Dawley yang telah digemukkan melalui HFD telah cuba dipulihkan dengan rawatan MLE 60 setiap kali selepas diberi makan HFD selama 12 minggu. Parameter yang sama seperti kajian pencegahan telah diukur. Selepas 9 minggu rawatan, tidak ada penurunan berat badan yang signifikan telah dicapai dalam mana-mana kumpulan yang dirawat, termasuk kumpulan yang dirawat dengan ubat kawalan standard Orlistat ®, walaupun kesan-kesan positif dapat diperhatikan pada adiposity, kandungan lemak di dalam tinja, lipid plasma, insulin dan tahap leptin. Rawatan pencegahan dan pemulihan obesiti dengan MLE 60 ke atas perubahan metabolik kemudiannya telah dikaji dengan terperinci menggunakan pendekatan berasaskan kaedah metabolomics ^{1}H NMR, yang mana air kencing dan serum di antara tikus gemuk dan kurus telah dibandingkan untuk mengenalpasti penanda biologi yang berkaitan dengan obesiti yang berpunca dari HFD. Analisis multivariat, termasuk unjuran kepada analisis struktur - diskriminan terpendam (OPLS-DA) telah digunakan untuk mengenalpasti penanda biologi. Pendiskriminasian terhadap metabolik yang merupakan produk pelbagai laluan metabolik, termasuk metabolisme glukosa dan kitaran TCA (lactate, 2- Oxoglutarate, sitrat, succinate, pyruvate , asetat), metabolisme asid amino (alanine , 2- hydroxybutyrate) , metabolisme choline (betaine), metabolisme kreatinin (creatinine) dan metabolisme mikrobiome usus (hippurate, phenylacetylglycine, dimethylamine, trigonelline). Rawatan dengan MLE 60, khususnya pada 250mg/kg , menyebabkan peningkatan yang ketara dalam pemindaan metabolik yang disebabkan oleh obesiti HFD seperti yang ditunjukkan oleh jarak antara kumpulan yang dirawat kepada kumpulan biasa di dalam plot skor OPLS -DA dan perubahan dalam trajektori daripada kumpulan berpenyakit ke arah kumpulan yang sihat apabila menerima rawatan. Kuantifikasi relatif terhadap metabolit yang telah didiskriminasi menunjukkan penambah baikan dalam kumpulan yang dirawat. Kajian ini melaporkan potensi kesan anti- obesiti oleh MLE 60, berdasarkan keupayaannya merencat aktiviti lipase seperti yang ditunjukkan oleh peningkatan kandungan lemak di dalam tinja dan kesan positifnya terhadap faktor-faktor penyebab obesiti termasuk leptin dan insulin. Ia juga mengesahkan bahawa pengambilan HFD menyebabkan perubahan terhadap metabolik selain daripada parameter yang telah dikaji secara tradisional sebelum ini, yang boleh diperbaiki melalui suplemen ekstrak tumbuhan seperti MLE 60 dan analisis berasaskan metabolomik ^{1}H NMR boleh menjadi alat yang cekap dalam penyelidikan berkaitan obesiti.

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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 Doctor of Philosophy. The members of the Supervisory Committee were as follows:

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LIST OF ABBREVIATION

AGRP	Agouti-Related Protein
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANOVA	One-Way Analysis of Variance
ARCP 30	Adipocyte Complement-related Protein
AST	Aspartate Aminotransferase
BAT	Brown Adipose Tissue
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
C/EBPα	CCAAT/enhancer Binding Protein-α
CART	Cocaine and Amphetamine-related Transcript
CPMG	Carr-Purcell-Meiboom-Gill
DPPH	2,2-Diphenyl-1-Picrylhyrazyl
EGCG	(-)- Epigallocatechin-3-Gallate
ELISA	Enzyme-linked Immunoabsorbent Assays
FDA	Food and Drug Administration
FFA	Free Fatty Acids
FTO	Fat Mass and Obesity Associated Genes
GCMS	Gas Chromatography Mass Spectroscopy
GFR	Glomerular Filtration Rate
GGT	γ- Glutamyltransferase
HDL	High Density Lipoprotein
HFD	High Fat Diet
HMBC	Heteronuclear-Multiple-Bond Correlation
HPLC	High Performance Liquid Chromatography
IDL	Intermediate Density Lipoprotein
LCMS	Liquid Chromatography Mass Spectroscopy
LDL	Low Density Lipoprotein
LPL	Lipoprotein Lipase
MLE	*Morinda citrifolia* leaf extract
MLE 60	*Morinda citrifolia* leaf extracted with 60% ethanol
MSH	Melanocyte Stimulating Hormone
MVDA	Multivariate Data Analysis
NAFLD	Nonalcoholic Fatty Liver Disease
ND	Normal Diet
NHMS	National Institutes of Health

NMR	Nuclear Magnetic Resonance
NPY	Neuropeptide Y
OPLS-DA	Orthogonal Projections to Latent Structures-Discriminant Analysis
PCA	Principal Component Analysis
PL	Pancreatic Lipase
PLS-DA	Partial Least Squares Discriminant Analysis
POMC	Anorexigenic pro-opiomelanocortin
PPAR-γ	Peroxisome Proliferator-activated Receptor- γ
SNP	Single Nucleotide Polymorphism
SUS	Shared and Unique Structure
TC	Total Cholesterol
TCA	Tricarboxylic Acid Cycle
TG	Triglycerides
TPC	Total Phenolics Compounds
TSP	3-Trimethylsilyl Propionic-2,2,3,3-d4 Acid Sodium Salt
VIP	Variable Importance in Project
VLDL	Very Low Density Lipoprotein
WAT	White Adipose Tissue
WHO	World Health Organisation

CHAPTER 1

INTRODUCTION

Obesity is a rapidly growing epidemic worldwide, presenting an increase in the risk of morbidity and mortality in many countries across the world. With more than 1.6 billion people being overweight worldwide and 500 million classified as obese, the World Health Organisation (WHO) has defined this escalating global epidemic as a condition of "globesity" (WHO, 2011). Forecasts predict that the unabated increase in obesity will continue and by 2030, there would be a 33% increase in the prevalence of obesity and 130% increase in severe obesity (Finkelstein et al., 2012). The problem of obesity is not confined to the industrialised and developed nations of the world. Even developing countries like Malaysia, has been affected. A period of 10 years showed a marked increase of 280% in the prevalence of obesity amongst those aged 18 years and above as compared to reports of the National Health and Morbidity Survey in 1996 (Rampal et al., 2007). More recent updates by Mohamud et al. (2011), reported the prevalence of overweight among adults to be 33.6% and 19.5% for obesity, with Malaysian females being more obese (22.5%) than their male counterparts (14.1%).

Complications associated with obesity including hypertension, hyperlipidemia, diabetes mellitus, cardiovascular disease, cancers and metabolic disorders have made it vital to discover new strategies and long-term solutions for weight management and control (Ferraro et al., 2002; Mukherjee, 2003). The use of medication and pharmaceuticals in the management of obesity is highly controversial and does not address the long-term nature of the problem. The current clinical treatment for obesity is a synthetic analogue of Lipstatin, Orlistat®, a gastrointestinal lipase inhibitor that competes with dietary fats for sites on the lipase molecules and has been shown to block the absorption of about 30% of dietary fat at a therapeutic oral dose of 120 mg three times a day (Hadvary et al., 1988). With the removal of several anti-obesity drugs on the European market, such as Sibutramine and Rimonabant, clinicians have no other options but to prescribe Orlistat®, despite side effects reported. The most common reported side effects are soft and oily stools, inconsistent defecation and impaired absorbance of fat soluble vitamins (Hill et al., 1999).

Most cases of human obesity are the result of an imbalance in calorie intake and energy expenditure, such as high fats diets and the interaction with the environment and lifestyles. Although reduction of caloric intake by diet and increased level of physical activity are the best approaches for weight loss, patients' compliance is inconsistent, justifying the need for better drugs and other non-conventional strategies such as the use of complementary and alternative medicines including herbal therapies (Wong et al., 2012).

More than 80% of the world population relies on traditional medicine for their primary health care (WHO, 2011). In the US alone, the natural health products market was worth $15 billion in the year 2000, with 16% of the population taking herbal remedies together with medical prescriptions (Kaufman et al., 2002). Over the

counter slimming aids with claims of being natural and effective are also popular (Blank et al., 2001). However there has been growing concerns on the risks associated with herbal slimming remedies, whose effectiveness claims are often not substantiated by scientific studies (Corns and Metcalfe, 2002; Jordan and Haywood, 2007). Therefore there is a need to combine convential analysis with a more robust technique providing a dataset which reflects what is actually happening in a biological system in terms of obesity induced abnormalities and the effect of therapeutic agents.

Significance of the study

The field of natural product research has undergone several positive changes over the years. It is established that improved technology such as proteomics, transcriptomics and genomics offer the platform to bridge traditional medicine and molecular pharmacology (Wang et al., 2005), assess bioactivity of traditional products (Yuliana et al., 2011) and study the biochemical effects on bioactive compounds on human subjects (Solanky et al., 2003). The most recent and new field of "omics" research has been defined as metabolomics, which is concerned with the high throughput identification and quantification of small molecule (< 1500 Da) metabolites in the metabolome (German et al., 2005) using analytical techniques such as nuclear magnetic resonance (NMR) spectroscopy or mass spectrometry (MS).

Although the use of metabolomics as a platform in obesity research is still in its infancy, it is being applied to many other areas of biomedical research. Kaddurah-Daouk et al. (2008), proposed the concept of pharmacometabolomics: the need to bridge well defined phenotypes with detailed genotypic data and using metabolomics concepts to elucidate mechanisms of diseases and drug actions as well as adverse effects. This approach has been to some extent applied to obesity research, whereby Kim et al. (2009) used ^{1}H- nuclear resonance spectroscopy (NMR) to assess metabolites in rat model of obesity induced by a high-fat diet (HFD). Metabolomics therefore, offers the opportunity to contribute on the understanding of the metabolic perturbations in the development of a HFD induced obesity and assesses the effect of therapeutic agents through the identification of altered metabolic pathways.

Malaysia, being a tropical country, has an extensive flora, which represents an untapped potential for natural compounds discovery. *Morinda citrifolia* L. *(*Rubiaceae), locally known as "mengkudu", has been used in folk remedies for over 2000 years. All parts of the plants, which include fruits, leaves, bark and roots have been shown to contain bioactive compounds that have high medicinal values. Medical applications have been reported for diabetes, infections, hypertension and cancer (Dixon et al., 1999). Previously the potential anti-obesity effect of *M. citrifolia* L. was reported through an inhibitory effect on lipoprotein lipase activity (Pak Dek et al., 2008), pancreatic lipase activity (Gooda Sahib et al., 2012) and on 3T3-L1 preadipocytes differentiation (Gooda Sahib et al., 2011). The leaf, root and fruit extracts of this plant exhibited antidyslipidemic effects in high fat induced dyslipidemia in rats (Mandukhail et al., 2010). However, there are no reported studies on the anti-obesity effects of this plant in high fat diet induced obesity *in vivo*.

This thesis hypothesizes that HFD induced obesity in an animal model will be associated with several perturbations in serum biochemistry and metabolic pathways and the leaves of *M. citrifolia* L. will exhibit therapeutic efficacy *in vivo*. It is anticipated that a ^{1}H NMR metabolomics approach combined with appropriate multivariate data analysis will be a good technique to study these perturbations and the therapeutic effect of *M. citrifolia* L. leaf extract.

Objectives

1. To characterise extracts of *M. citrifolia* L. leaves, of different maturity and extracted with different ethanol concentrations, in terms of their bioactive compounds and bioactivity, *in vitro*
2. To assess the effect of *M. citrifolia* L. leaf in the prevention of obesity in lean Sprague- Dawley rats fed a high fat diet *in vivo*
3. To assess the effect of *M. citrifolia* L. leaf in the amelioration of obesity in high fat diet induced obese Sprague- Dawley rats *in vivo*
4. To analyse the metabolic perturbations of HFD induced obesity in a rat model and the therapeutic effects of *M. citrifolia* L. through the identification of biomarkers metabolites using a ^{1}H NMR based metabolomics approach

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