



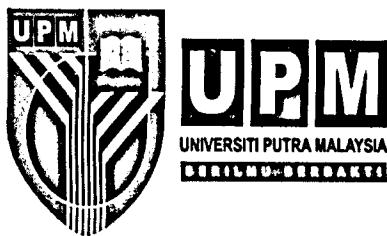
UNIVERSITI PUTRA MALAYSIA

***BLOOD GLUCOSE RESPONSE AND CELLULAR CHANGES
ASSOCIATED WITH ANDROGRAPHOLIDE TREATMENT IN INSULIN-
RESISTANT MICE***

HANAA ABDULABBAS ABDULAMEER

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By

HANAA ABDULABBAS ABDULAMEER

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

January 2017

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DEDICATION

To my dear mother, and my brothers who encouraged and supported me throughout my study, my life partner and the supporter of my studies, Hassan Mohammed Jasim and my children, Zaid, Ahmed and Ali who are the most expensive things in my life



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

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January 2017

Chairman : Associate Professor Goh Yong Meng, PhD
Faculty : Veterinary Medicine

The continual increase in the incidence of insulin resistance and its associated metabolic syndrome has necessitated the thrust for the development of therapeutic agents that could ameliorate this condition. It occurs when the normal circulating concentration of insulin fails to regulate the body glucose homeostasis. Insulin resistance has been common sequelae of obesity; insulin-resistant syndrome implies a series of abnormalities that frequently happen in insulin-resistant individuals. Available therapeutic agents and or medications to combat insulin resistance are not without several limitations including side effects. The need for a newer agent that could ameliorate insulin resistance with minimal or no side effect is therefore a global necessity.

Although the use of andrographolide for therapeutic purposes has gained wide acceptability, it's usage in the treatment of prediabetic or insulin resistance condition that is associated with type 2 diabetes has not been evaluated. Moreover, the studies about the effect of andrographolide on insulin resistance still few and no study demonstrated the effect of andrographolide on ultrastructural changes that related with insulin resistance disorder.

This study was undertaken to investigate pure on the andrographolide potential to ameliorate impaired glucose tolerance and insulin resistance in high fat diet male mice. The mice were fed with high-fat diet (45% dietary energy from fat) for 24 weeks to induce insulin resistance. Upon confirmation of insulin resistance, these mice were then divided into four groups of 12 mice each. The control negative group (CN) received normal chow and three high-fat diet groups, which were; control positive group HFD (CP), high-fat diet group with andrographolide at 25 mg/kg (HFA25), and high-fat diet with andrographolide at 50 mg/kg (HFA50).

Alternatively, the results in present study are illustrated after 15 days treatment with andrographolide. Andrographolide treatment groups (HFA25, HFA50) had significantly ($P<0.05$) reduced the body weight, fasting serum glucose levels, intraperitoneal glucose tolerance test (IPGTT) and intraperitoneal insulin tolerance test (IPIIT). Also we determined the effect of andrographolide significant ($P<0.05$) reduced on the corresponding area under the curve of glucose (AUC_g), the area under the curve of insulin (AUC_i), the insulin resistance index and HbA_{1c} levels. Blood lipid profile tests, TAG, VLDL, gamma-glutamyl transferase GGT, liver enzymes (AST, ALT, ALP), leptin, resistin, oxidative stress malonaldehyde (MDA), kidney function tests (BUN, albumen, creatinine, total protein), pro-inflammatory cytokines (TNF α , IL-1 β , IL-1 α , IL-6, MCP-1 and NF- κ B), leptin, adiponectin and anti-oxidant activities (SOD, CAT, and GSH) were significantly reduced ($P<0.05$). In the CP group those tests quantified significant higher ($P<0.05$) before and post andrographolide treatment. In addition to that, blood glucose and insulin level were recorded significant decrease ($P<0.05$).

On the other hand, there are detectable evident about ameliorative changes of andrographolide exerted on through histological sections, immunohistochemistry sections, ultrastructural examinations and gene expressions in the pancreas, liver, skeletal muscle, adipose tissue and kidney of treated male mice. Results showed the HFA50 group had the greatest histological, immunohistochemical, ultrastructural and gene expressions significant ($P<0.05$) reduced changes on regeneration cell injuries, reduced inflammation, macrophage cell infiltrations of pancreatic cells, liver, adipose, and kidney. Whereas, the HFA25 group showed significant ($P<0.05$) least decrease in histological, immunohistochemical, ultrastructural and gene expressions changes that include regeneration of cell injuries, reduced inflammation, and macrophage cell infiltrations of pancreatic cells, liver, adipose and kidney. Importantly, this result were attended with a significant ($P<0.05$) tissues healing sings (increased in some and large size rough endoplasmic reticulum, increased secretory granules of pancreas tissue and increased the number of mitochondria in the HFA50 group and least extent the HFA25group compared to the CP group. Furthermore, we observed a significant differences ($P<0.05$) in some gene expressions between treated groups. The HFA50 appeared significant ($P<0.05$) down-regulation of cytokines and interleukins genes expressions (TNF α , IL-1 β , IL-1 α , IL-6, MCP-1 and NF- κ B). In contrast, up regulation of GLUT4, GLUT1, PPAR α , PPAR γ and SREBPs genes expressions. While, the HFA25 appeared least gene expressions changes compared to the CP group.

Overall, our results concluded that the anti-insulin resistance effect seen in andrographolide treatment is associated with restoration of insulin sensitivity and alleviated pathological changes in the pancreas, liver, adipose and kidney tissues. It is possible that andrographolide has potential capability to direct cellular regeneration through anti-pro-inflammatory cytokines inhibition and increase glucose transporter gene expressions at the cellular levels.

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

**GERAKBALAS GLUKOSA DARAH DAN PERUBAHAN SEL BERIKUTAN
RAWATAN ANDROGRAPHIOLIDE PADA MENCIT YANG MENGALAMI
KERINTANGAN INSULIN**

Oleh

HANAA ABDULABBAS ABDULAMEER

Januari 2017

Pengerusi : Profesor Madya Goh Yong Meng, PhD
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Peningkatan insiden kerintangan insulin berserta sindrom metabolik yang berkaitan telah mendorong usaha pembangunan agen terapeutik yang boleh memperbaiki keadaan ini. Kerintangan insulin berlaku apabila tahap insulin yang normal tidak berkesan dalam pengawalaturan homeostasis glukosa darah. Rintangan insulin adalah sekuela dari obesiti; sindrom tahan-insulin yang melibatkan siri-siri keabnormalan yang sering berlaku pada individu tahan insulin. Agen terapeutik dan atau ubatan yang ada untuk melawan rintangan insulin adalah tidak tanpa limitasi-limitasi dan termasuk juga kesan sampingan. Oleh itu, keperluan untuk agen yang lebih baru yang boleh memperbaiki rintangan insulin dengan kesan minimum atau tiada kesan sampingan adalah satu keperluan global. Walaupun penggunaan andrographolide untuk tujuan terapeutik telah diterima secara luas, penggunaannya dalam rawatan untuk keadaan prediabetik atau rintangan insulin yang dikaitkan dengan diabetes jenis 2 belum lagi dinilai. Penyelidikan ini bertujuan untuk mengkaji potensi andrographolide dalam memperbaiki toleransi glukosa dan rintangan insulin pada mencit jantan yang mempunyai diet lemak tinggi. Mencit telah diberi makan dengan diet tinggi lemak (45% tenaga makanan dari lemak) untuk 24 minggu untuk mencetus rintangan insulin. Setelah pengesahan rintangan insulin dicapai, mencit ini kemudiannya dibahagikan kepada empat kumpulan dengan 12 mencit setiap satu kumpulan. Satu kumpulan kawalan negatif (CN) menerima makanan normal dan manakala tiga kumpulan lagi berdiet tinggi lemak iaitu; kumpulan kawalan positif HFD (CP), kumpulan diet tinggi lemak dengan andrographolide pada 25 mg/kg (HFA25), dan diet tinggi lemak dengan andrographolide pada 50 mg / kg (HFA50). Keputusan dalam kajian ini di ambil selepas 15 hari rawatan dengan andrographolide. Kumpulan rawatan Andrographolide (HFA25, HFA50) telah mengurangkan secara signifikan ($P < 0.05$) pada berat badan, paras glukosa serum puasa, ujian toleransi glukosa, intraperitoneal (IPGTT) dan ujian toleransi insulin intraperitoneal (IPITT). Kajian juga telah menentukan kesan andrographolide secara signifikan ($P < 0.05$) dalam mengurangkan rangkuman luas kawasan di bawah keluk untuk glukosa (AUCg), kawasan di bawah

keluk insulin (AUC_i), indeks rintangan insulin dan paras HbA1c. Manakala nilai-nilai di dalam ujian profil lipid darah, TAG, VLDL, gamma-glutamyl transferase GGT, enzim hepar (AST, ALT, ALP), leptin, resistin, tekanan oksidatif malonaldehid (MDA), ujian fungsi buah pinggang (BUN, albumen, kreatinin, protein total), sitokin pro-imflamasi (TNF α , IL-1 β , IL-1 α , IL-6, MCP-1 dan NF-KB), leptin, adiponectin dan anti-oksida aktiviti (SOD, CAT dan GSH) telah dikurangkan dengan ketara ($P<0.05$). Dalam kumpulan CP, nilai-nilai dalam ujian-ujian tersebut adalah lebih tinggi ($P<0.05$) selepas rawatan dengan andrographolide. Di samping itu, glukosa darah dan tahap insulin telah mencatatkan penurunan yang signifikan ($P<0.05$). Terdapat bukti-buktii menunjukkan rawatan andrographolide yang memberi perubahan positif dapat dikesan pada irisan histologi, imunohistokimia, pemeriksaan struktur ultra dan ekspresi gen pankreas, hepar, otot skeletal, tisu adipos dan ginjal mencit jantan yang dirawat. Kumpulan HFA50 menunjukkan bukti penyembuhan yang paling ketara dari segi histologi, imunohistokimia dan struktur ultra dan ekspresi gen secara signifikan ($P<0.05$) mengurangkan perubahan pada regenerasi sel selepas kecederaan, mengurangkan imflamasi, serta menunjukkan infiltrasi sel makrofaj pada sel pankreas, hepar, adipos dan ginjal. Manakala, kumpulan HFA25 menunjukkan paling rendah perubahan ($P<0.05$) pada histologi, immunohistokemikal, struktur ultra dan perubahan ekspresi gen yang mana termasuk regenerasi selepas kecederaan sel, imflamasi dikurangkan, dan infiltrasi sel makrofaj pada sel-sel pankreas, hepar, adipos dan ginjal. Hasil penting dalam kajian, didapati bahawa keputusan signifikan ($P<0.05$) pada penyembuhan tisu (peningkatan dalam beberapa retikulum endoplasma kasar saiz besar, peningkatan granul rembesan tisu pankreas dan peningkatan bilangan mitokondria dalam kumpulan HFA50 manakala kumpulan HFA25 mempunyai nilai-nilai paling rendah berbanding dengan kumpulan CP. Tambahan lagi, kajian telah mendapat perbezaan yang signifikan ($P<0.05$) pada beberapa ekspresi gen di antara kumpulan-kumpulan yang dirawat. Kumpulan HFA50 menunjukkan signifikan ($P<0.05$) dalam kawalaturan-menurun terhadap sitokin dan interleukin ekspresi gen (TNF α , IL-1 β , IL-1 α , IL-6, MCP-1 dan NF- κ B) tetapi kawalaturan-menaik untuk ekspresi gen GLUT4, GLUT1, PPAR α , PPAR γ and SREBP. Manakala kumpulan HFA25 pula menunjukkan ekspresi gen paling rendah berbanding kumpulan CP. Secara keseluruhan, keputusan kajian membuat kesimpulan bahawa kesan anti kerintangan insulin yang dilihat dalam rawatan andrographolide dikaitkan dengan pemulihan sensitiviti insulin dan peningkatan perubahan patologi pada tisu pankreas, hepar, adipos dan ginjal. Andrographolide berkemungkinan berpotensi untuk mengarauhkan regenerasi sel melalui perencutan anti pro-imflamatori sitokin dan meningkatkan ekspresi gen yang bertanggungjawab dalam pengangkutan glukosa di peringkat sel.

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Declaration by graduate student

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LIST OF ABBREVIATIONS

ACC	Acetyl CoA
AG	Andrographolide
<i>A.p</i>	<i>Andrographis paniculata</i>
ALT	Alanine amino transferase
AMPK	Adenosine monophosphate dependent kinase
ANOVA	Analysis of variance
AST	Aspartate amino transferase
ATP	Adenosine triphosphate
AUC	Area under the curve
BCD	Butter plus chow diet
cAMP	cyclic adenosine monophosphate
CAT	Catalase
CD	Chow diet
DAG	Diacylglycerol
DM	Diabetes mellitus
DW	Distal water
FFA	Free fatty acid
EGP	Endogenous glucose production
ELISA	Enzyme linked immuno sorbent assay
G1P	Glucose 1 phosphate
G6P	Glucose 6 phosphate
G6Pase	<i>Glucose 6phosphatase</i>
GLUT	Glucose transporter
GLUT1	Glucose transporter substrate 1

GLUT4	Glucose transporter substrate 4
GSH	Glutathione S transferase
H2O2	Hydrogen peroxide
HbA1c	Hemoglobin A1c
HDL	High density lipoprotein
HDL-C	High density lipoprotein cholesterol
HO	Hydroxyl radical
Hr	Hour
HRP	Horseradish peroxidase
IDDM	Insulin dependent diabetes mellitus
ip	Intra peritoneal
JNKs	c-Jun N-terminal kinase
IL1- α	Interleukin-1 alfa
IL1- β	Interleukin-1 beta
IL-6	Interleukin-6
IKK	Inhibitor kappa kinase
IPGTT	Intraperitoneal glucose tolerance test
IPITT	Intraperitoneal insulin tolerance test
IR	Insulin resistance
IRSs	Insulin receptor substrate
IRS-1	Insulin receptor substrate -1
Kcal	Kilocalorie
kg	Kilogram
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein cholesterol

MAP	Mitogen activated pathway
MCP1	Macrophage chemoattractant
MDA	Malondialdehyde
mg	Milligram
min	Minutes
MAPK	Mitogen-activated protein kinase
mL	Milliliter
mmol	Milimole
mTOR	Mammalian target of rapamycin
N	Normal
NADH	Nicotinamide adenine dinucleotide phosphate
NF- κ B	Nuclear factor Kappa beta
ng	Nano gram
NHMS	National Health and Morbidity Survey
NIDDM	Non-insulin dependent diabetes mellitus
nM	Nano meter
PBS	Phosphate buffer saline
PDE3B	Phosphodiesterase 3B
PDK	Phosphoinositide dependent kinase
PEG	Polyethylene glycol
PEPCK	Phosphoenolpyruvate carboxy kinase
PGs	Prostaglandins
PI3K	phosphatidylinositol 3 kinase
PIP2	Phosphatidylinositol di-phosphate
PIP3	Phosphatidylinositol tri-phosphate

PKA	Protein kinase A
PKB	Protein kinase B
PKC	Protein kinase C
POD	Per oxidase
PPAR γ	Peroxisome proliferator Receptor gamma
PPAR α	Peroxisome proliferator Receptor alfa
ROS	Reactive oxygen species
RNS	Reactive nitrogen species
SEM	Standar error of the mean
SFA	Saturated fatty acids
SOCS3	Suppressor of cytokine signaling-3
SOD	Superoxide dismutase
TAG	Triacyl glycerol
T2DM	Type 2 diabetes mellitus
TLR4	Toll-like receptor 4
TNF α	Tumor necrosis factor-alfa
VLDL	Very low-density lipoprotein
UPR	unfolded protein response
WHO	World Health Organization
μ l	Microliter
TBARS	Thiobarbituric acid reacting substances

CHAPTER 1

INTRODUCTION

In recent years, insulin resistance has garnered more attention, not only because it precludes type-2 diabetes (T2DM), but is also as a risk factor that augments the risk for cardiovascular diseases such as coronary heart disease and hypertension (Saltiel et al., 2001; Lee et al., 2011). When these two diseases coexist, it is referred to as, metabolic syndrome, and it is predicted that an estimated 250 million people worldwide will be affected with T2DM by the year 2020 (Wan-Nazaimoon et al., 2013). Even though the primary factors that cause this disease are still unknown, there is an indication that insulin resistance plays a vital role in the development of these metabolic diseases (Trout et al., 2007).

Insulin resistance is an important indicator of the dysregulation of glucose metabolism. A survey in 2006 revealed that there are more than 371 million people worldwide that are affected by diabetes, of which in Malaysia, about 1.2 million adults aged from 30 years and above are affected. From this number, it is estimated that approximately 98% of Malaysians with diabetes suffer from T2DM (Wan-Nazaimoon et al., 2013). Approximately 1 in 3 Malaysians are suffering from, or at risk of being diabetic. This number has continuously increased every year over the past 5 years as shown in the National Health and Morbidity Survey conducted in 2011 (Letchuman et al., 2010). It is assessed that by 2020, Malaysia will have approximately 4.5 million people with diabetes.

The state of insulin resistance occurs when normal insulin production does not correspond with the insulin response by the body. Hence, any defect of the insulin-signalling pathway can in fact lead to insulin resistance (Kahn, 2005a; Lee et al., 2011).

The public has the misconception that insulin resistance only occurs in people who are overweight or those with high levels of sugar intake. In fact, insulin resistance can also occur in individuals who have a normal weight and of any age group. Insulin resistance can be prevented and even reversed by reverting to a healthy lifestyle by eating healthy and incorporating an exercise regime (Adiels et al., 2008; Al batran et al., 2014).

Insulin resistance is on the rise because of the poor dietary balance and lack of physical activity among affluent societies of the 21st century. Early human societies since the beginning of time, focused on hunting and gathering food, and this simple act comprised of two key elements: obtaining wholesome foods straight from the environment and exercising in the process of gathering food. In modern societies, since food is so readily available, it has led to reduced physical movement. Furthermore, modern processed foods have less nutritional value and most contain

highly refined carbohydrates, preservatives, pesticides, trans-fats, toxins and high amounts of sugar, which are factors that can potentially contribute to insulin resistance (Draznin, 2006; Asrih et al., 2015).

The onset of insulin resistance can be prevented or reversed by understanding the role of insulin in regulating the uptake of glucose in the body. It is crucial to recognize the role of dietary factors, such as fatty acids and their inter-relationships with insulin resistance (Centres of Disease Control and Prevention, 2011; Furman, 2015). The findings will be invaluable, as they will potentially elucidate how body fats and visceral body composition play a role in the regulation of blood glucose, as well as understanding the potential changes in the pancreas, liver and kidney when insulin resistance sets in. The mouse model of diet-induced obesity has become one of the most valuable tools for understanding the relationship between a HFD and the development of insulin resistance (Cardinal et al., 1998; Bastard et al., 2006).

Although there are available drugs that enable an individual with prediabetic conditions to lead a normal life, these drugs can have serious side effects. Medicines that decrease insulin resistance contain α -glucosidase inhibitors, Biguanides like metformin, sulphonylureas and Thiazolidinediones (Baudrand et al. 2014; Widharna, 2015 and Sugden, 2004). Therefore, alternative traditional medicinal plants have garnered more attention in recent years. Many traditional medicinal plants have been used for T2DM therapy (Devasagayam, 2007), one such plant is *Andrographis paniculata* (Burm.f.) Nees (Acanthaceae). *A. paniculata* (Figure 1.1) is a traditional medicinal plant commonly found in South-East Asia, India and Indo-China. Andrographolide is the major diterpenoid found in *A. paniculata*, making up about 4%, 0.8~1.2% and 0.5~6% in dried whole plants, stem and leaf extracts, respectively (Burgos et al., 1997). Andrographolide derivatives have been demonstrated to have anti-hyperlipidaemic, anti-hyperglycemic and β -cell protective effects in animals (Zhang et al., 2000). Orally administered extract of *A. paniculata* was able to prevent glucose-induced hyperglycemia in non-diabetic rabbits (Borhanuddin et al., 1994). Andrographolide appears to reduce plasma glucose concentration in a dose-dependent manner in streptozotocin-induced diabetes and normal rats, with the prospective effect observed in normal rats rather than in diabetic rats (Yu et al., 2003).



Figure 1.1 : *Andrographis paniculata* plant (Mishra et al., 2007).

A recent study effectively demonstrated that andrographolide has undeniably potent hypolipidemic effects (Yang et al., 2012), and protects the cardiovascular system with non-significant liver damage by lowering TC, TAG, VLDL-TC and LDL-TC in mice. The purified extract of andrographolide in rats was reported to have significantly decreased the levels of blood glucose, TC and LDL with T2DM (Nugroho et al., 2012). Most of the studies up to date on andrographolide have focused on *A. paniculata* extract and its effect on diabetic conditions induced by streptozotocin (Subramanian et al., 2008; Dandu et al., 2009; Nugroho et al., 2012b).

The present study was carried out to assess the effects of andrographolide on blood glucose, insulin with histopathology, ultrastructural alteration and gene expression in insulin resistant male mice. It was hypothesized that, andrographolide agent would a reduce blood glucose levels and hyperinsulinemia while alleviating the cellular changes that are associated with insulin resistance in the male mice. This would have occurred through changes associated with tissue regeneration and restoration of mechanism that regulate blood glucose.

Therefore, the objectives of the study were:

- i- To investigate the effects of andrographolide treatment on blood glucose and insulin sensitivity in the mice model.
- ii- To investigate the histopathological, immunohistological changes in the pancreas, liver, adipose tissue and kidney tissues before and after treatment with andrographolide compound.
- iii- To investigate the effects andrographolide compound on the ultrastructural changes (pancreas, liver) in insulin resistant male mice.

To investigate changes in the inflammatory, lipid and glucose function markers in insulin resistant male mice following andrographolide treatment.

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