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ANTIDIABETIC ACTIVITY OF Curculigo latifolia EXTRACTS IN IN VITRO AND IN VIVO STUDIES

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By

NUR AKMAL BINTI ISHAK

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

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Abstract of thesis presented to the Senate of Universiti Putra Malaysia in Fulfillment of the Requirements for the degree of Doctor of Philosophy

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January 2014

Chairman : Professor Maznah Ismail, PhD

Faculty : Institute of Bioscience

Curculigo latifolia (*C. latifolia*) plant grows wildly in tropical Asia especially in Malaysia. *C. latifolia* fruit has 9000 times the sweetness of sucrose. The sweet taste of *C. latifolia* fruit is due to a protein known as curculin. This indicates that *C. latifolia* plant has the potential to be used as an alternative low-calorie sweetener for diabetic patients. Besides, natural phenolic compounds contained in *C. latifolia* which posses antioxidant activity can also be used to prevent and treat diabetes. In the present study, antidiabetic properties of *C. latifolia* in cell lines (*in vitro*) and in diabetic-induced rats were determined.

Different parts of *C. latifolia* plant (fruit, root and leaf) were extracted using distilled water and then were freeze dried into powder. Total phenolic content and free radicals scavenging activity of *C. latifolia* fruit, root and leaf extracts were determined. *C. latifolia* fruit and root extracts exhibited higher scavenging free radicals activity (1.0 mg/ml) and followed by leaves extract (1.2 mg/ml). Besides, *C. latifolia* fruit extracts showed high phenolic content (95 mg GAE/100 g extract) and followed by roots (90 mg GAE/100 g extract), leaf in hot (100^{o}C) water (83 mg GAE/100 g extract) and leaf in normal (at room temperature) water (74 mg GAE/100 g extract). In *in vitro* study, different concentrations (0.01, 0.025, 0.05, 0.1, 0.5, 1.0 and 3 mg/ml) of *C. latifolia* fruit, root and leaf extracts were screened for cytotoxicity effect towards BRIN- BD11 pancreatic, L6 myotubes and 3T3 adipocytes cells using 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H tetrazolium) (MTS) assay. Results showed that *C. latifolia* fruit and root extracts did not cause toxicity towards BRIN-BD11 pancreatic, L6 myotubes and 3T3 adipocytes cells. However, *C. latifolia* leaf extracts at 2.3 mg/ml caused 50% BRIN BD11 cell death. Furthermore, the effect of *C. latifolia* as potential antidiabetic agent was evaluated by measuring: (1) insulin secretion by BRIN-BD11 pancreatic cells (2) radio labelled 2-Deoxy-D-glucose (2DOG) uptake by 3T3 adipocyte and L6 myotubes and (3) adiponectin secretion by 3T3 adipocytes. Results from insulin assay showed that *C. latifolia* roots extract increased 40% of insulin over basal secretion followed by *C. latifolia* fruits extract (35%) in BRIN BD11 pancreatic cells. Whereas, leaves extract did not show significant increment.

Meanwhile, results from 2DOG uptake activity showed that *C. latifolia* fruits extract significantly increased (p<0.05) 2DOG activity with insulin present up to 13 fold (at 0.05 mg/ml) in 3T3 adipocytes and 16 fold (at 0.1 mg/ml) in L6 myotubes. However, *C. latifolia* roots extract at 0.05 mg/ml significantly increased (p<0.05) 2DOG activity without insulin presence up to 2 fold in 3T3 adipocytes and L6 myotubes. Present study also indicates that with insulin presence, C. *latifolia* leaves extract at 0.1 mg/ml increased 21 fold of adiponectin secretion. However without insulin presence, *C. latifolia* roots extract increased 6 fold adiponectin secretion.

The effectiveness of *C. latifolia* fruit and root extracts in increasing insulin secretion, 2DOG uptake and adiponectin secretion *in vitro* study were then confirmed by study on diabetes-induced rats. Combination of *C. latifolia* fruit and root (1:1) v/v used to treat the diabetes-induced rats. Diabetes rats were developed by feeding high fat diet (HFD) which contained 56.9% calorie contributed by fat and low dose (40 mg/kg bw) STZ injection. After acclimation period, rats were fed high fat diet for 30 days and were then injected with 40 mg/kg bw of STZ via intravenous (iv) injection at the tail. Rats were divided into seven groups; 1) normal rats, 2) obese rats (only fed with HFD), 3) diabetic rats (induced with HFD and low dose STZ), 4) diabetic rats treated with 50 mg/kg b.w of *C. latifolia* fruit:root (1:1) extracts, 5) diabetic rats treated with 100 mg/kg b.w of *C. latifolia* fruit:root extracts, 6) diabetic rats treated with 200 mg/kg b.w of *C. latifolia* fruit:root extracts and 7) diabetic rats treated with 10 mg/kg b.w of glibenclamide. Treatment period was 30 days. Before and after treatments, biochemical parameters such as glucose, insulin, adiponectin, total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL), triglycerides (TG), urea, creatinine, alanine aminotransferase (ALT) and plasma γ-glutamyltransferase (GGT) were measured. Results showed that 200 mg/kg b.w of *C. latifolia* fruit:root extracts reduced significantly (p<0.05) 65% plasma glucose and 49% of total cholesterol level. Besides, with the same concentration it also increased 12% insulin and 41% of adiponectin levels in plasma. Furthermore, 50, 100 and 200 mg/kg b.w of *C. latifolia* fruit:root extracts showed that urea, creatinine, ALT and GGT levels in diabetic-induced rats were reduced towards normalcy after 30 days of treatment.

The regulatory effects of *C. latifolia* fruit:root extracts on genes involved in glucose and lipid metabolisms were further studied. Ten genes; IGF-1, IRS-1, GLUT4, PPARγ, PPARα, AdipoR1, AdipoR2, leptin, lipoprotein lipase and lipase were analyzed using GenomeLab GeXP Genetic Analysis System. Results showed that treatment with 200 mg/kg b.w of *C. latifolia* fruit:root extracts effectively improved glucose metabolism in diabetic-induced rats due to increase expression of insulin signaling receptor (IRS-1 (4 fold) and IGF-1 (4 fold)), glucose transporter (GLUT 4 (2 fold)) and peroxisome proliferator-activated receptor (PPARγ (8 fold) and PPARα (2 fold)). It also showed to improve lipid metabolism by increasing the expression of adiponectin receptor (AdipoR1 (5 fold) and AdipoR2 (4 fold)), leptin (5 fold), lipase (3 fold) and lipoprotein lipase (2 fold).

Based on the current findings, it can be concluded that *C. latifolia* fruit:root extracts exhibit antidiabetic properties due to higher total phenolic content and its ability to scavenge free radicals. It effectively improved glucose and lipid metabolisms in diabetic-induced rats by increased IGF-1, IRS-1, GLUT4, PPARγ, PPARα,

AdipoR1, AdipoR2, leptin, lipoprotein lipase and lipase genes regulation. All of the results demonstrate potential use of *C. latifolia* in diabetic therapy.

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

KAJIAN AKTIVITI ANTIDIABETIK OLEH EKSTRAK *Curculigo latifolia* KE ATAS KULTUR SEL DAN TIKUS

Oleh

NUR AKMAL BINTI ISHAK

Januari 2014

Pengerusi : Profesor Maznah Ismail, PhD

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Curculigo latifolia (*C. latifolia*) tumbuh dengan liar di Asia Tropika terutamanya di Malaysia. Buah *C. latifolia* didapati 9000 kali rasa manis sukrosa. Rasa manis buah *C. latifolia* adalah disebabkan oleh protein yang dikenali sebagai curculin. Ini menunjukkan bahawa *C. latifolia* berpotensi digunakan sebagai pemanis alternatif yang rendah kalori untuk pesakit diabetes. Selain itu, sebatian fenolik semulajadi yang terkandung di dalam *C. latifolia* yang mengandungi aktiviti antioksida juga boleh turut digunakan untuk mencegah dan merawat diabetes. Dalam kajian ini, ekstrak *C. latifolia* telah digunakan untuk menentukan sifat antidiabetik *C. latifolia* di dalam sel (*in vitro*) dan pada tikus yang diaruhkan diabetik.

Pelbagai bahagian-bahagian pokok *C. latifolia* (buah, akar dan daun) diekstrak menggunakan air suling dan kemudiannya disejukkeringkan menjadi serbuk. Jumlah kandungan fenolik dan aktiviti memerangkap radikal bebas oleh ekstrak buah, akar dan daun *C. latifolia* telah ditentukan. Ekstrak buah dan akar *C. latifolia* menunjukkan lebih tinggi aktiviti memerangkap radikal bebas (1.0 mg / ml) dan diikuti oleh ekstrak daun (1.2 mg / ml). Selain itu, ekstrak buah *C. latifolia* juga mengandungi kandungan fenolik yang tinggi (95 mg GAE/100 g ekstrak) dan diikuti oleh akar (90 mg GAE/100 g ekstrak), ekstrak daun dalam air panas (100^{o}C) (83 mg GAE/100 g ekstrak) dan ekstrak daun dalam air biasa (pada suhu bilik) (74 mg GAE/100 g ekstrak). Dalam kajian *in vitro*, kepekatan ekstrak buah, akar dan daun *C. latifolia* yang berbeza (0.01, 0,025, 0.05, 0.1, 0.5, 1.0 dan 3 mg/ml) telah disaring untuk mengesan sitotoksik ke atas sel pankreatik BRIN-BD11, L6 miotub dan 3T3 adiposit menggunakan asai 3-(4,5-dimetilthiazol-2-YL)-5-(3-karboksimetoksifenil)-2-(4-sulfofenil)-2H-tetrazolium) (MTS). Keputusan menunjukkan bahawa ekstrak buah dan akar *C. latifolia* tidak menyebabkan toksik ke atas sel-sel pankreatik BRIN-BD11, L6 miotub dan 3T3 adiposit. Walau bagaimana pun, ekstrak daun *C. latifolia* pada kepekatan 2.3 mg/ml menyebabkan kematian sel BRIN-BD11 sebanyak 50%. Tambahan pula, kesan *C. latifolia* sebagai agen antidiabetik telah dikaji dengan mengukur: (1) insulin yang dirembeskan oleh pankreatik BRIN-BD11, (2) pengangkutan radio label 2-Deoxy-D-glukosa (2DOG) oleh 3T3 adiposit dan L6

miotub dan (3) adiponektin yang dirembeskan oleh 3T3 adiposit. Keputusan daripada asai insulin menunjukkan bahawa ekstrak akar *C. latifolia* meningkatkan 40% rembesan insulin lebih daripada rembesan basal diikuti oleh ekstrak buah *C. latifolia* (35%) dalam BRIN-BD11 pankreatik sel. Manakala, ekstrak daun tidak menunjukkan peningkatan yang ketara. Sementara itu, keputusan daripada aktiviti pengambilan 2DOG menunjukkan bahawa ekstrak buah *C. latifolia* meningkatkan dengan ketara ($p<0.05$) aktiviti 2DOG dengan kehadiran insulin sehingga 13 kali ganda (pada 0.05 mg/ml) dalam 3T3 adiposit dan 16 kali ganda (pada 0.1 mg/ml) dalam L6 miotub. Walaupun demikian, ekstrak akar *C. latifolia* pada 0.05 mg/ml meningkatkan dengan ketara ($p<0.05$) aktiviti 2DOG tanpa kehadiran insulin sehingga kepada 2 kali ganda dalam 3T3 adiposit dan L6 miotub. Kajian ini juga menunjukkan bahawa dengan kehadiran insulin, ekstrak daun *C. latifolia* pada 0.1 mg/ml meningkatkan 21 kali ganda rembesan adiponektin. Bagaimanapun tanpa kehadiran insulin, ekstrak akar *C. latifolia* meningkatkan 6 kali ganda rembesan adiponektin.

Keberkesanan ekstrak buah dan akar *C. latifolia* dalam meningkatkan rembesan insulin, pengangkutan 2DOG dan rembesan adiponektin di dalam kajian *in vitro* kemudiannya telah disahkan melalui kajian ke atas tikus yang diaruh diabetis. Kombinasi ekstrak buah dan akar (1:1) *C. latifolia* telah digunakan untuk merawat tikus yang diaruh diabetis melalui diet yang tinggi lemak (HFD) yang mengandungi kalori 56.9% disumbangkan oleh lemak dan suntikan STZ berdos rendah (40 mg/kg bw). Selepas tempoh penyesuaian, tikus telah diberi makan diet yang tinggi lemak selama 30 hari dan kemudiannya disuntik dengan 40 mg/kg b.w STZ melalui suntikan (iv) intravena pada ekor. Tikus telah dibahagikan kepada tujuh kumpulan; 1) tikus normal, 2) tikus obes (hanya diberi makan dengan HFD), 3) tikus diabetik (diaruhkan dengan HFD dan STZ berdos rendah), 4) tikus diabetik yang dirawat dengan 50 mg/kg b.w ekstrak buah:akar (1:1) *C. latifolia*, 5) tikus diabetik yang dirawat dengan 100 mg/kg b.w ekstrak buah:akar *C. latifolia*, 6) tikus diabetik yang dirawat dengan 200 mg/kg b.w ekstrak buah:akar *C. latifolia* dan 7) tikus diabetik yang dirawat dengan 10 mg/kg b.w glibenclamide. Tempoh rawatan adalah 30 hari. Sebelum dan selepas rawatan, parameter biokimia seperti plasma glukosa, insulin, adiponektin, jumlah kolesterol, lipoprotein berketumpatan tinggi (HDL), lipoprotein berketumpatan rendah (LDL), trigliserida (TG), urea, kreatinin, alanine aminotransferase (ALT) dan γ-glutamyltransferase (GGT) diukur. Keputusan menunjukkan bahawa 200 mg/kg b.w ekstrak buah:akar *C. latifolia* menurunkan dengan ketara ($p<0.05$) paras plasma glukosa sebanyak 65% dan 49% jumlah kolesterol. Di samping itu, dengan kepekatan yang sama ia juga meningkatkan paras plasma 12% insulin dan 41% adiponektin. Tambahan pula, 50, 100 dan 200 mg/kg b.w ekstrak buah:akar *C. latifolia* menunjukkan bahawa tahap urea, kreatinin, ALT dan GGT dalam tikus yang diaruhkan diabetik telah dikurangkan ke tahap sediakala selepas 30 hari rawatan.

Kesan pengawalaturan ekstrak buah:akar *C. latifolia* ke atas gen yang terlibat dalam metabolisme glukosa dan lipid telah dikaji pada tikus yang diaruh diabetis. Sepuluh gen; IGF-1, IRS-1, GLUT4, PPARγ, PPARα, AdipoR1, AdipoR2, leptin, lipoprotein lipase dan lipase dianalisis menggunakan Sistem Analisis Genetik GenomeLab GeXP. Keputusan menunjukkan bahawa rawatan dengan 200 mg/kg b.w ekstrak buah:akar *C. latifolia* berkesan memperbaiki metabolisma glukosa secara berkesan ke atas tikus yang diaruhkan diabetik disebabkan oleh peningkatan ekspresi reseptor

isyarat insulin (IRS-1 (4 kali ganda) dan IGF-1 (4 kali ganda)), pengangkut glukosa (GLUT 4 (2 kali ganda)) dan reseptor peroksisom-proliferator (PPARγ (8 kali ganda) dan PPARα (2 kali ganda)). Ia juga menunjukkan peningkatan metabolisma lipid dengan meningkatkan reseptor adiponektin (AdipoR1 (5 kali ganda) dan AdipoR2 (4 kali ganda)), leptin (5 kali ganda), lipase (3 kali ganda) dan lipoprotein lipase (2 kali ganda).

Berdasarkan dapatan semasa, kesimpulannya bahawa ekstrak buah:akar *C. latifolia* menunjukkan sifat antidiabetik disebabkan oleh jumlah kandungan fenolik yang tinggi dan kebolehannya memerangkap radikal bebas. Ia berkesan meningkatkan metabolisme glukosa dan lipid dalam tikus yang diaruh diabetis melalui laluan AMPK dan PI3K dengan meningkatkan pengawalaturan gen IGF-1, IRS-1, GLUT4, PPARγ PPARα, AdipoR1, AdipoR2, leptin, lipoprotein lipase dan lipase. Semua keputusan menunjukkan potensi *C. latifolia* sebagai agen untuk terapi diabetik.

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I certify that a Thesis Examination Committee has met on 27 January 2014 to conduct the final examination of Nur Akmal binti Ishak on her thesis entitled "Antidiabetic Activity of *Curculigo latifolia* Extracts in *In Vitro* and *In Vivo* Studies" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the Doctor of Philosophy.

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This thesis was submitted to the Senate of the 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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DECLARATION

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LIST OF ABBREVIATIONS

AdipoR1	Adiponectin receptor 1
AdipoR2	Adiponectin receptor 2
AGE	Advanced glycation end-product
ALT	Alanine aminotransferase
AMPK	AMP-activated protein kinase
ATP	Adenosine triphosphate
CO_2	Carbon dioxide
CVD	Cardiovascular disease
DEPC	Diethyl pyrocarbonate
DM	Diabetes mellitus
DNA	Deoxyribonucleic acid
ELISA	Enzyme-linked immunosorbent assay
ER	Endoplasmic reticulum
FFA	Free fatty acid
FRIM	Forest Research Institute Malaysia
G-6-Pase	Glucose-6-phosphatase
GGT	Gamma glutamyltransferase
GI	Glycaemic index
GLP-1	Glucagon-like peptide-1
GLUT	Glucose transporter
HbA1c	Glycated hemoglobin
HDL	High density lipoprotein

HFD	High fat diet
HOMA	Homeostasis model assessment-estimated
ICA	Islet cell antibody
ID	Idiopathic
IDDM	Insulin dependent diabetes mellitus
IDF	International Diabetes Federation
IFG	Impaired fasting glucose
IGF-1	Insulin-like growth factor-1
IGT	Impaired glucose tolerance
IL-6	Interleukin-6
IRS	Insulin receptor substrate
LDL	Low density lipoprotein
MARDI	Malaysian Agricultural Research and Development Institute
MODY	Maturity onset diabetes of the young
MUFA	Monosaturated fatty acids
NIDDM	Non-insulin dependent diabetes mellitus
NPCB	National Pharmaceutical Control Bureau
NPD	Normal pallet diet
PCR	Polymerase chain reaction
PEPCK	Phosphoenolpyruvate

	carboxykinase
PPAR	Peroxisome proliferator-activated receptor
PUFA	Polyunsaturated fatty acids
RNA	Ribonucleic acid
SAFA	Saturated fatty acids
SD	Sprague-Dawley
STZ	Streptozotocin
TG	Triglycerides
TNF-α	Tumor necrosis factor-α
TZD	Thiazolidinediones
UPM	Universiti Putra Malaysia
VLDL	Very low density lipoprotein
WHO	World Health Organization

CHAPTER 1

INTRODUCTION

1.1 Background of Study

Diabetes mellitus (DM) is a metabolic disorder which has become one of the major worldwide health issues. World Health Organization (WHO) (2006) has classified DM into two major types which are type 1 and type 2 according to clinical stages and aetiological types. Type 1 DM referred to -cell destruction in which insulin is required and it also known as insulin-dependent diabetes mellitus (Tuomi, 2005). 0HDQZKLOH 0RQQLHU HW DO V S H F L I I F D O O \ G I dysfunction, insulin resistance and excess of glucose production from liver. Insulin resistance is referred to impaired insulin-mediated glucose clearance into peripheral tissues. As this disease progresses, it will damage other tissues and can lead towards several complications such as cardiovascular diseases, nephropathy, retinopathy and neuropathy (Steinberger and Daniels, 2003).

The incidence of Type 2 DM has become a worldwide epidemic and according to the International Diabetes Federation (IDF) (2012) report, there are approximately 366 million people who are suffering from this disease. It is projected that the global prevalence could reach 567 million by 2030 if no urgent action is taken. The highest rate of diabetes are found in India with a current figure of 40.9 million and followed by China with 39.8 million. Furthermore, Pakistan, Japan, USA, Russia and Germany are also widely affected by diabetes (IDF, 2012). Data from National Diabetes Statistics (2011) indicate that the total prevalence of diabetes in the United State is 25.8 million where 18.8 million people have been diagnosed and another 7 million people are undiagnosed. Meanwhile, people with prediabetes are approximately 79 million. The statistics also indicate that 215,000 adolescents under 20 years are diagnosed to be diabetic. Furthermore, diabetes prevalence affects 10.9 million adults aged 65 years and above in the US (National Diabetes Statistics, 2011).

Diabetes prevalence in Malaysia has been showing an upward trend. As at 2006, there were 1.5 million people aged 18 years and above who were diagnosed with type 2 DM (National Diabetes Institution, 2006). According to the third National Health and Mobility Survey (NHMS III) in 2006, diabetes prevalence among rural and urban areas significant increased from 10.5% to 12.1%. Meanwhile, diabetes prevalence among patients 18 years and above was 11.6%, while it was 14.9% in patients 30 years and above. The survey also indicated that Indians had the highest diabetes prevalence (19.9%) followed by Malays (11.9%) then Chinese (11.4%). However, there were no differences based on gender or income status (Zanariah et al., 2006). This survey indicated that diabetes was growing in Malaysia and interventions were needed to curb the rising trend.

Lifestyle, dietary composition and genes are determined to be major factors that affect both diabetes development and complications (Kontogianni et al., 2012; Weber and Narayan, 2008; Chan et al., 2007). Shift from traditional lifestyle to

urban lifestyle has changed mankind activity. According to Leahy (2005), watching television too much, less physical activity, wide availability of cars and abundance of high calorie foods are the current problem in modern living. High calorie foods such as fat have greatly affect the development of diabetes where it influences glucose metabolism by defective cell membrane function, insulin signaling, enzyme activity and gene expression (Risérus et al., 2009). Studies based on interaction between nutrient and genetic is known as nutrigenomic. Furthermore, interaction between nutrient and genetic makeup can affect physiological changes in human where nutrient influences the genes during transcription process (Trujillo et al., 2006). In T2DM, influence of nutrient and environmental factors in genetic predisposition involves multiple genes (Kaput et al., 2007). Some genes are involved in insulin signaling pathway such as glucose transporter 4 (GLUT4), insulin (INS) and insulin receptor (INSR), glucose homeostasis pathway such as glucose transporter 2 and 4 (GLUT 2 and GLUT4), glucose-6-phosphatase (G6PC) and lipoprotein metabolism such as peroxisome proliferator- D F W L Y D W H G U H F H S W R U / 3 3 $ 5 . 3 3 $ 5 D Q G 3 3 $ 5 / 3 K L O O L S V H W D O

Understanding the pathogenesis of T2DM has provided information to the scientists to find a better approach in preventing and treating diabetic problem. Changing bad lifestyle habit into mild exercise is a pre-treatment for the diabetic patient. Through exercise, excess weight can be reduced by increasing the energy expenditure. Thus, insulin sensitivity and glucose tolerance will improve (Hu and Manson, 2003). Meanwhile, taking quality diet which composes of low fat, high fiber and several micronutrients are recommended in order to prevent and treat T2DM (Franz et al., 2003). Apart from that, several alternative sweeteners such as aspartame, saccharin, cyclamate and acesulfame-K are another approach that can be used to treat diabetes. These alternative sweeteners are substitutes from natural and some are artificial. Besides, it has less-calorie and non-nutritive value (Bastaki, 2005). Hence, it could reduce energy intake among diabetic patient. Apart from that, alternative sweeteners also have high intensity of sweet taste property and due to this property it becomes preferable choice among diabetic patients. They only need to take a small amount of it to make their meal taste sweet.

In addition to exercise and dietary management, pharmaceutical approach can also be used to treat type 2 DM. At present time, therapeutic drug has been used to treat diabetes through multiple target sides. To date, there are five major classes of therapeutic drug and it had been classified according to their mechanism of action; V X O I R Q \ O X U H D V E L J X D Q L G H V W K L D] R G L G L Q H G L R Q H glucosidase inhibitor. Each of these drugs has their own mode of actions to treat diabetes either through reduction of glucose absorption in intestinal, improve insulin secretion or triggering PPAR (Patel et al., 2012). However, according to Bastaki (2005), combination of two drugs such as metformin and sulfonylurea can increase the hypoglycemic activity where it treats diabetes through two modes of action. Despite of antidiabetic drugs effectiveness, prolong usage of it will cause adverse effect.

Besides using alternative sweeteners and antidiabetic drugs, natural products are also used in treating diabetes. There are several plants that posses medicinal properties and approximately 800 plants have been identified with antidiabetic properties (Warjeet Singh, 2011). Studies have reported that these plants have the ability to reduce blood glucose and improve insulin secretion (Dheer and Bhatnagar, 2010).

Meanwhile, according to Malviya et al. (2010), secondary metabolites from plant such as phenolic, alkaloids and glycosides are the one which implicate as having antidiabetic effect. Among those secondary metabolites, phenolic compounds are the one which abundantly present in plants and demonstrated having antioxidant, antidiabetic and antiobesitiy properties (Randhir and Shetty, 2007).

0DODVLD LV ULFK ZLWK QDWXUDO UHVRXUFHV DQG biodiversity-rich countries (Ang, 2004; Institute for Medical Research, 2002). There are about 1300 plants that have been used as traditional medicine (Jantan, 2004). Every part of the plant has been used and obtains active component which exhibit therapeutic effect. *Curculigo latifolia* plant is belonging to Hypoxidaceae family. It is a shrub tree and it can be found in the west Malaysia (Mohd Firdaus et al., 2010). *C. latifolia* is also called Lemba or Lumbah among local community in Malaysia. Traditionally, it has been used as sweetener in drinks (Chooi, 2006). This shrub tree consists of berry-like fruit and this fruit exhibits both sweet tasting and taste modifying activities (Kant, 2005). Curculin and neoculin have been identified as proteins that possess those activities (Ibuka et al., 2006). Despite *C. latifolia* is sweet and can be use as alternative sweetener for diabetic patient, there is no scientific study on *C. latifolia* as antidiabetic agent.

1.2 Significant of Study

There are many adverse side effects of using artificial and synthetic sweetener. It causes several complications such as brain tumors, hallucinations, seizures and bladder cancer (Renwick, 2006; Academy of Nutrition and Dietetics, 2012). The controversy about the side effect of therapeutic drugs and alternative sweetener has already drawn the attention of researchers to look for natural nutraceutical and nature sweeteners which are more effective and less toxic (Okokon et al., 2012; Jia et al., 2009). The sweet taste of *C. latifolia* fruit has been applied and used as sweetener in chewing gum, drinks and meals (Kurihara and Nirasawa, 1994). However, the use of *C. latifolia* as sweetener for diabetic patient is not well studied. It can be expected as a new replacement for table sugar and synthetic sweeteners.

Apart from adverse side effects of synthetic sweetener, prolong consumption of GLDEHWLF GUXJV FRXOG DOVR DIIHFW SDWLHQWV¶ KH colleagues (2001), sulfonylureas cause hypoglycemia, increase in body weight, gastrointestinal (GI) disturbance and headache to the user. Besides, metformin has been reported to cause abdominal pain, diarrhea, nausea and lactic acidosis to the diabetic patient (Nzerue et al., 2003). Other diabetic drug that cause adverse side effect is thiazolidinediones where it causes hepatoxicity after prolong usage (Amori et al., 2007). Apart from adverse side effect, antidiabetic drug also has limited mode of action. Available diabetic drugs only show single mode of action in treating diabetes and it needs to combine with another class of antidiabetic drug to make these drugs more efficient such as combination of metformin and sulfonylurea (Bastaki, 2005).

Despite of using synthetic sweeteners and drugs, natural souces have become alternative choices for diabetic patients. This is because it is affordable and less toxic (Singh et al., 2007). Several plants have been identified and showed antidiabetic

properties. However, there is no study has been done on *C. latifolia* extracts towards type 2 diabetes. Therefore, this study was conducted to determine the effect of *C. latifolia* extracts in *in vitro* and *in vivo*. In *in vitro* study, total phenol compounds and antioxidant properties of *C. latifolia* fruit, root and leaf extracts were determined. Then, these extracts were tested on cell lines (BRIN-BD11 pancreatic, 3T3 adipocytes and L6 myotubes) to determine mode of *C. latifolia* antidiabetic action either through cytokine (insulin and adiponectin) secretions or glucose uptake. Meanwhile in *in vivo* study, combination of *C. latifolia* fruit and root extracts were used to assess antidiabetic effect on diabetic-induced rats. Furthermore, the interaction of *C. latifolia* fruit:root extracts on regulatory genes in glucose and lipid metabolisms were also determined.

The rising number of diabetic patients have urged researches to find more effective diabetic treatment. Treating diabetic problems at early stage without cause complication at prolong usage is preferable. A major target in current study is to identify novel strategies to overcome diabetic problems based on natural sources which contain antidiabetic properties. Besides, finding from this study also give some opportunities to develop new nutraceutical and pharmaceutical products from indigenous plants. This is the reason why this study should be carried out successfully.

1.3 Objectives of the Study

1.3.1 General Objective

The main objective of this study was to investigate the antidiabetic properties of *C. latifolia* extract on diabetes *in vitro* and *in vivo*.

1.3.2 Specific Objectives

1. To determine total phenolic contents and free radical scavenging activity of *C. latifolia* extracts.

2. To determine antidiabetic properties of *C. latifolia* extracts through insulin secretion in BRIN BD11 cells and adiponectin secretion in 3T3 adipocytes.

3. To determine antidiabetic properties of *C. latifolia* extracts through glucose uptake activity in 3T3 adipocyte and L6 myotubes.

4. To investigate the antidiabetic and hypolipidemic properties of *C. latifolia* fruit:root extracts in a diabetic model (*in vivo*).

5. To determine the interaction between *C. latifolia* fruit:root extracts with insulin signaling genes in diabetic model.

1.4 Hypotheses of the Study

1. The *C. latifolia* fruit and root extracts exhibit high total phenolic content and scavenging activity.
2. The *C. latifolia* fruit and root extracts exhibit antidiabetic properties by increase insulin secretion in BRIN BD11 and adiponectin secretion in 3T3 adipocyte.
3. The *C. latifolia* fruit and root extracts exhibit antidiabetic properties by increase glucose uptake activity in 3T3 adipocyte and L6 myotubes.
4. The *C. latifolia* fruit:root (1:1) extract possess antidiabetic and hypolipidemic properties by treating diabetic problem in diabetic model.
5. The *C. latifolia* fruit:root (1:1) extract trigger up regulation of insulin signaling genes in diabetic model.

REFERENCES

Abhilash, M., Sauganth Paul, M. V., Varghese, M. V., Harikumaran Nair, R. (2011). Effect of long term intake of aspartame on antioxidant defense status in liver. *Food and Chemical Toxicology*. 49:1203-1207.

Abo, K. A., Fred-Jaiyesimi, A. A. and Jaiyesimi, A. E. A. (2008). Ethnobotanical studies of medicinal plants used in the management of diabetes mellitus in South Western Nigeria. *Journal of Ethnopharmacology*. 115:67±71.

Abudula, R., Jeppesen P. B., Rolfsen S. E. D., Xiao J. and Hermansen K. (2004). Rebaudioside a potently stimulates insulin secretion from isolated mouse islets : studies on the dose-, glucose-, and calcium-dependency. *Metabolism*, 53:1378-1381.

Academy of Nutrition and Dietetics. (2012). Position of the Academy of Nutrition and Dietetics: Use of nutritive and nonnutritive sweeteners. *Journal of the Academy of Nutrition and Dietetics*. 112:739-758.

Afman, L. A. and Müller, M. (2012). Human nutrigenomics of gene regulation by dietary fatty acids. *Progress in Lipid Research*. 51:63±70.

Agamy, N. (2009). Effect of the natural sweetener (stevia) and the artificial sweetener (aspartame) on some biochemical parameters in normal and aloxan-induced diabetic rats. *New Biotechnology*. 25(1):12.

Ahima, R. S. and Flier, J. S. (2000). Adipose tissue as an endocrine organ. *Trends in Endocrinology and Metabolism*. 11:327±32.

Ahmed, A. M. (2002). History of diabetes mellitus. *Saudi Medical Journal*. 23:373-378.

Alasalvar, C. M, Al-Farsi, P. C., Quantick, F., Shahidi, R. and Wiktorowic, Z. (2005). Effect of chill storage and modified atmosphere packaging (MAP) on antioxidant activity, anthocyanins, carotenoids, phenolics and sensory quality of ready-to-eat shredded orange and purple carrots. *Food Chemistry*. 89:69-76.

Amarowicz, R., Pegg, R. B., Rahimi-Moghaddam, P., Barl, B. and Weil, J. A. (2004). Free-radical scavenging capacity and antioxidant activity of selected plant species from the Canadian prairies. *Food Chemistry*. 84:551-562.

American Diabetes Association (2005). Diagnosis and classification of diabetes mellitus. *Diabetes Care*. 28:37-42.

Amic, D., Davidovic-Amic, D., Beslo, D., Rastija, V., Lucic, B. and Trinajstic, N. (2007). SAR and QSAR of the Antioxidant Activity of Flavonoids. *Current Medical Chemistry*. 14: 827-845.

Amori, R. E., Lau, J. and Pittas, A. G. (2007). Efficacy and safety of incretin therapy in type 2 diabetes: systematic review and meta-analysis. *The Journal of the American Medical Association.* 298(2):194-206.

Anandharajana R., Jaiganesh S., Shankernarayanan N. P., Viswakarma R. A. and Balakrishnan A. (2006). In vitro glucose uptake activity of Aegles marmelos and Syzygium cumini by activation of Glut-4, PI3 kinase and PPAR*c* in L6 myotubes. *Phytomedicine.* 13:434-441.

Anderson, J. W., Randles, K. M., Kendall, C. W. and Jenkins, D. J. (2004). Carbohydrate and fiber recommendations for individuals with diabetes: a quantitative assessment and meta-analysis of the evidence. *Journal of the American College of Nutrition.* 23(1):5-17.

Ang, H. H. (2004). An insight into Malaysian herbal medicines. *TRENDS in Pharmacological Sciences*. 25:6.

Atoui, A. K., Mansouri, A., Boskou, G. and Kefalas, P. (2005). Tea and herbal infusions: their antioxidant activity and phenolic profile. *Food Chemistry*. 89:27-36.

Aybar, M., Riera, A. N. S., Grau, A. and Sanchez, S. S. (2002). Hypoglycemic effect of the water extract of *Smallanthus soncifolius* (yacon) leaves in normal and diabetic rats. *Journal of Ethnopharmacology*. 74:125-132.

Aziz, Z. and Tey, N. P. (2009). Herbal medicines: prevalence and predictors of use among Malaysian adults. *Complementary Therapies in Medicine*. 17(1):44-50.

Baichun, Y., Lihong, C., Ying, Q., James, A. T., Judi, A. M., Kevin, C., Lisa, G. C., Bajin, H., Robert, G., Jay, S., Kathleen, K. B., Stephen, A. S. and Greg, P. (2006). Changes of skeletal muscle adiponectin content in diet-induced insulin resistant rats. *Biochemical and Biophysical Research Communications.* 341:209-217.

Bailey, C. J. (2003). New approaches to the pharmacotherapy of diabetes. In: Pickup, J.C., William, G. (Eds.), Textbook of Diabetes, volume 2, third edition. Blackwell Science Ltd., UK, pp. 73.1-73.21.

Bakand, S., Hayes, A. and Winder, C. (2009). Development of *in Vitro* Methods for Toxicity Testing of Workplace Air Contaminants. *International Journal of Occupational Hygiene*. 1(1):26-33.

Balasundram, N., Sundram, K. and Samman, S. (2006). Analytical, Nutritional and Clinical Methods Phenolic compounds in plants and agri-industrial by-products: Antioxidant activity, occurrence, and potential uses. *Food Chemistry*. 99:191-203.

Bansal, P., Paul, P., Mudgal, J., Nayak, G., Thomas, P.S., Priyadarsini, K.I, et al. (2011). Antidiabetic, antihyperlipidemic and antioxidant effects of the flavonoid rich fraction of Pilea microphylla L. in high fat diet/streptozotocin-induced diabetes in mice. *Experiment Toxicology and Pathology*. doi:10.1016/j.etp.2010.12.009.

Barnett, A. (2003). Management of lipids in patients with diabetes. *Diabetes Obesity Metabolism.* 5(1):3-9.

Barroso, I. (2005). Genetics of type 2 diabetes. *Diabetes Medicine*. 22:517-535.

Bastaki, S. (2005). Diabetes mellitus and its treatment. *International Journal Diabetes and Metabolism*. 13:111-134.

Baudry, A., Lamothe, B., Bucchini, D., Jami, J., Montarras, D., Pinset, C. and Joshi, R.L. (2001) IGF-1 receptor as an alternative receptor for metabolic signaling in insulin receptor-deficient muscle cells. *Federation the European Biochemical Societies Letter*. 488:174-178.

Berg, A. H., Combs, T. P., and Scherer, P. E. (2002). ACRP30/adiponectin: an adipokine regulating glucose and lipid metabolism. *Trends in Endocrinology Metabolism*, 13: 84±89.

Bhandari, M.R., Anurakkun1-+RQJ*DQG.DZDEDWD-. -Glucosidase and . -amylase inhibitory activities of Nepalese medicinal herb Pakhanbhed (*Bergenia ciliata, Haw*.). *Food Chemistry*. 106:247-252.

Boden, G., Chen, X. and Stein T., P. (2001). Gluconeogenesis in moderately and severely. *Biology*. 359:148-158.

Bolkent, S., Yanardag, R., Bolkent, S. and Doger, M. M. (2004). Beneficial effects of combined treatment with niacin and chromium on the liver of hyperlipemic rats. *Biological Trace Element Research*. 101:219-230.

Bolzán, A. D. and Bianchi, M. S. (2002). Genotoxicity of streptozotocin. *Mutation Research*. 512:121-34.

Bordenave, S., Brandou, F., Manetta, J., Fédou, C., Mercier, J. and Brun, J.F. (2008). Effects of acute exercise on insulin sensitivity, glucose effectiveness and disposition index in type 2 diabetic patients. *Diabetes and Metabolism*. 34:250-257.

Boule, N.G., Haddad, E., Kenny, G.P., Wells, G.A. and Sigal, R.J. (2001). Effects of exercise in glycemic control and body mass in type 2 diabetes mellitus. A meta-analysis of controlled clinical trials. *The Journal of the American Medical Association*. 286:1218-1227.

Briaud, I., Harmon, J.S., Kelpe, C.L., Segu, V.B. and Poitout, V. (2001) lipotoxicity of the pancreatic beta-cell is associated with glucose esterification of fatty acids into neutral lipids. *Diabetes*. 50:315-321.

Brouns, F., Bjorck, I., Frayn, K. N., Gibbs, A. L., Lang, V., Slama, G. and Wolever, T. M. S. (2005). Glycaemic index methodology. *Nutrition Research Reviews*. 18:145-171.

Bryant, N. J., Govers, R. and James, D. E. (2002). Regulated transport of the glucose transporter GLUT4. *Natural Review Molecular Cell Biology*. 3:267-277.

Cakir, A., Mavi, A., Yildirim, A., Duru, M. E., Harmandar, M. and Kazaz, C. (2003). Isolation and characterization of antioxidant phenolic compounds from the aerial parts of Hypericum hyssopifolium L. by activity-guided fractionation. *Journal of Ethnopharmacology*. 87:73-83.

Canto, C., Jiang, L. Q., Deshmukh, A. S., Mataki, C., Coste, A., Lagouge, M., Zierath, J. R. and Auwerx, J. (2010). Interdependence of AMPK and SIRT1 for metabolic adaptation to fasting and exercise in skeletal muscle. *Cell Metabolism*. 11:213-219.

Chakrabarti, R., Damarla, R. K. B., Mullangi, R., Sharma, V. M., Vikramadithyan, R. K. and Rajagopalan, R. (2006). Insulin sensitizing property of *Indigofera mysorensis* extract. *Journal of Ethnopharmacology*. 105(2):102-106.

Chan, L. C. K., Ware, R., Kesting, J., Marczak, M., Good, D. and Shaw, J. T. E. (2007). Short term efficacy of a lifestyle intervention programme on cardiovascular health outcome in overweight Indigenous Australians with and without type 2 diabetes mellitus: The healthy lifestyle programme (HELP). *Diabetes Research and Clinical Practice*. 75(1):65-71.

Chatterjee, M.N. and Shinde, R. (2002). Text book of medical biochemistry. Jaypee Brothers.

Chavez, J.A. and Summers, S.A. (2010). Lipid oversupply, selective insulin resistance, and lipotoxicity: Molecular mechanisms. *Biochimica et Biophysica Acta*. 1801:252-265.

Cheel, J., Theoduloz, C., Rodríguez, J. A., Peter, D.S. and Caligari, G. (2007). Free radical scavenging activity and phenolic content in achenes and thalamus from

Fragaria chiloensis ssp. *chiloensis*, *F. vesca* and *F.* x *ananassa* cv. Chandler. *Food Chemistry*. 102(1):36-44.

Chen, D. and Wang, M.W. (2005). Development and application of rodent models for type 2 diabetes. *Diabetes, Obesity and Metabolism*. 7:307±317.

Chena, C., Hsiang, C.Y., Chiang, A. N., Loe, H. Y. and Li, C. I. (2010). Peroxisome proliferator-activated receptor gamma transactivation-mediated potentiation of glucose uptake by Bai-Hu-Tang. *Journal of Ethnopharmacology*. 118:46±50.

Chinetti, G., Lestavel, S., Bocher, V., Remaley, A.T., Neve, B., Torra, I. P.,Teissier, E., Minnich, A., Jaye, M., Duverger, N., Brewer, H. B., Fruchart, J.C., Clavey, V. and Staels, B. (2001). PPAR-alpha and PPAR-gamma activators induce cholesterol removal from human macrophage foam cells through stimulation of the ABCA1 pathway. *Nature Medicine.* 7(1):53-8.

Choi, S.B., Park, C.H., Choi, M.K., Jun, D.W. and Park, S. (2004). Improvement of insulin resistance and insulin secretion by water extracts of *Cordyceps militaris*, *Phellinus linteus*, and *Paecilomyces tenuipes* in 90% pancreatectomized rats. *Bioscience, Biotechnology, and Biochemistry.* 68:2257-2264.

Choi, S.W., Benzie, I. F. F., Ma, S. W., Strain, J. J. and Hannigan, B. M. (2008). Acute hyperglycemia and oxidative stress: Direct cause and effect? *Free Radical Biology and Medicine.* 44:1217-1231.

Chooi, O. H. (2006). Tumbuhan liar: khasiat ubatan dan kegunaan lain. Utusan Publications and Distributors Sendirian Berhad, Kuala Lumpur, p. 116.

Chung, J. H., Manganiello, V. and Dyck, J. R. B. (2012). Resveratrol as a calorie restriction mimetic: therapeutic implications. *Trends in Cell Biology*. 22:10

Clarke, S.D. (2004). The multi-dimensional regulation of gene expression by fatty acids: polyunsaturated fats as nutrient sensors. *Current Opinion Lipidology*. 15:13-8.

Clee, S.M. and Attie, A.D. (2006). The genetic landscape of type-2 diabetes in mice. *Endocrinology Reviews.* 28:48-83.

Clemmons, D.R. (2007). Modifying IGF1 activity: an approach to treat endocrine disorders, atherosclerosis and cancer. *Natural Review Drug Discovery*. 6:821-833.

Cnop, M., Welsh, N., Jonas, J.C., Jorns, A., Lenzen, S. and Eizirik, D.L. (2005). Mechanisms of pancreatic beta-cell death in type 1 and type 2 diabetes: many differences, few similarities. *Diabetes*. 54(2):97-107.

Combs, T.P., Berg, A.H., Obici, S., Scherer, P.E. and Rossetti, L. (2001). Endogenous glucose production is inhibited by the adipose-derived protein Acrp30. *Journal Clinical Investigation*. 108:1875-1881.

Cordell, G. A. and Colvard, M. D. (2005). Some thoughts on the future of ethnopharmacology. *Journal of Ethnopharmacology*. 100:5-14.

Costacou, T. and Mayer-Davis, E. J. (2003). Nutrition and prevention of type 2 diabetes. *Annual Review of Nutrition*. 23:147-170.

Dagon, Y., Avraham, Y. and Berry, E. M. (2006). AMPK activation regulates apoptosis, adipogenesis, and lipolysis by eIF2*a* in adipocytes. *Biochemical and Biophysical Research Communications*. 340:43-47.

Dhar M. S., Yuan J. S., Elliott S. B. and Sommardahl C. (2006). A type IV P-type ATPase affects insulin-mediated glucose uptake in adipose tissue and skeletal muscle in mice. *Diabetes.* 54(2):40-45.

Dheer, R. and Bhatnagar, P. (2010). A study of the antidiabetic activity of Barleria prionitis Linn. Indian. *Journal of Pharmacology*. 42:70-73.

Diabetes and Nutrition Study Group of the European Association for the Study of Diabetes. (2000). Recommendations for the nutritional management of patients with diabetes mellitus. *European Journal Clinical Nutrition*. 54:353-355.

Diez. J. J. and Iglesias, P. (2003). The role of the novel adipocyte-derived hormone adiponectin in human disease. *European Journal Endocrinology*.148:293-300.

'LPRSRXORV9:DVVRQ0*UHHQ&DQG+XQGDO6+7KH33$5/DJRQLVW GW501516, promotes fatty acid oxidation but has no direct effect on glucose utilisation or insulin sensitivity in rat L6 skeletal muscle cells. *Federation the European Biochemical Societies Letters.* 581:4743-4748.

Dzamko, N.L. and Steinberg, G.R. (2009). AMPK-dependent hormonal regulation of wholebody energy metabolism. *Acta Physiology*. (Oxf) 196:115-127.

Eknoyan, G. and Nagy, J. (2005). A history of diabetes mellitus or how a disease of the kidneys evolved into a kidney disease. *Advance Chronic Kidney Disease*. 12:223-229.

Eldor, R. and Raz, I. (2006). Lipotoxicity versus adipotoxicity-The deleterious effects of adipose tissue on beta cells in the pathogenesis of type 2 diabetes. *Diabetes Research and Clinical Practice*. 74:3-8.

El-Serag, H.B., Tran, T., Everhart, J.E., (2004). Diabetes increases the risk of chronic liver disease and hepatocellular carcinoma. *Gastroenterology*. 126:460-468.

Elsner, M., Guldbakke, B., Tiedge, M., Munday, R. and Lenzen, S. (2000). Relative importance of transport and alkylation for pancreatic beta-cell toxicity of streptozotocin. *Diabetologia*. 43:1528-1533.

Esposito, K., Maiorino, M.I., Ceriello, A. and Giugliano, D. (2010). Prevention and control of type 2 diabetes by Mediterranean diet: A systematic review. *Diabetes Research and Clinical Practice.* 89:97-102.

Fenech, M., El-Sohemy, A., Cahill, L., Ferguson, L. R., French, T. C., Tai, E. S., Milner, J., Koh, W., Xie, L., Zucker, M., Buckley, M., Cosgrove, L., Lockett, T., Fung, K. Y. C. and Head, R. (2011). Nutrigenetics and nutrigenomics: viewpoints on the current status and applications in nutrition research and practice. *Journal of Nutrigenetics and Nutrigenomics.* 4(2):69-89.

Ferrannini, E. and Mari, A. (2004). Beta cell function and its relation to insulin action in humans: a critical appraisal. *Diabetologia*. 47:943-56.

Flanagan, A. M. Brown, J. L. Santiago, C. A. Aad, P. Y. Spicer, L.J. and Spicer, M. T. (2008). High-fat diets promote insulin resistance through cytokine gene expression in growing female rats. *The Journal of Nutritional Biochemistry*. 19(8):505-513.

Fogarty, S. and Hardie, D. G. (2010). Development of protein kinase activators: AMPK as a target in metabolic disorders and cancer. *Biochimica et Biophysica Acta*. 1804:581-591

Fonseca-Alaniz, M.H., Takada, J., Alonso, M.I.C., Lima, F.B. (2007). Adipose tissue as an endocrine organ: from theory to practice. *Journal Pediatria*. 83(5):192-203.

Fonseca, V. (2006). The role of basal insulin therapy in patients with type 2 diabetes mellitus. *Insulin*. 1(2):51-60.

Fontana, L., Eagon, J.C., Trujillo, M.E., Scherer, P.E., Klein, S. (2007). Visceral fat adipokine secretion is associated with systemic inflammation in obese humans. *Diabetes*. 56:1010-1013.

Forouhi, N. G. and Wareham, N.J. (2010). Epidemiology of diabetes. *Medicin*e. 38:11-19.

Franconi, F., Seghieri, G., Canu, S., Straface, E., Campesi, I and Malorni, W. (2008). Are the available experimental models of type 2 diabetes appropriate for a gender perspective? *Pharmacological Research*. 57(1):6±18.

Franz, M. J., Bantle, J. P., Beebe, C. A., Brunzell, J. D., Chiasson, J. L., Garg, A. (2003). Evidence based nutrition principles and recommendations for the treatment and prevention of diabetes and related complications. *Diabetes Care*. 26:51-61.

Fritz, T., Wandell, P., Aberg, H. and Engfeldt, P. (2006). Walking for exercise - does three times per week influence risk factors in type 2 diabetes? *Diabetes Research and Clinical Practice*. 71:21-27.

Frode, T.S. and Medeiros Y.S. (2008). Animal models to test drugs with potential antidiabetic activity. *Journal of Ethnopharmacology.* 115:173-183.

Frojdo, S., Durand, C., Molin, L., Carey, A. L., El-Osta, A., Kingwell, B. A., Febbraio, M. A., Solari, F., Vidal, H. and Pirola, L. (2011). Phosphoinositide 3-kinase as a novel functional target for the regulation of the insulin signaling pathway by SIRT1. *Molecular and Cellular Endocrinology.* 335(2):166-176.

Frojdo, S., Vidal, H. and Pirola, L. (2009). Alterations of insulin signaling in type 2 diabetes: a review of the current evidence from humans. *Biochim Biophys Acta*. 1792:83-92.

Fruhbeck, G., Gomez-Ambrosi, J., Muruzabal, F. J., and Burrell, M. A. (2001). The adipocyte: A model for integration of endocrine and metabolic signaling in energy metabolism regulation. *American Journal Physiology Endocrinology Metabolism*. 280:827-847.

Fujii, N., Jessen, N. and Goodyear, L.J. (2006). AMP-activated protein kinase and the regulation of glucose transport. *American Journal of Physiology and Endocrinology Metabolism*. 291:867-877.

Gadsby, R. (2002). Epidemiology of diabetes. *Advanced Drug Delivery Reviews*. 54:1165-1172.

Gastaldelli, A. (2011). Role of beta-cell dysfunction, ectopic fat accumulation and insulin resistance in the pathogenesis of type 2 diabetes mellitus. *Diabetes Research and Clinical Practice*. 93:60-65.

Gastaldelli, A., Ferrannini, E., Miyazaki, Y., Matsuda M and DeFronzo, R. A. (2004). Beta-cell dysfunction and glucose intolerance: results from the San Antonio metabolism (SAM) study. *Diabetologia*. 47:31-9.

Gastaldelli, A., Ferrannini, E., Miyazaki, Y., Matsuda, M. andDeFronzo, R.A. (2004). San Antonio metabolism study. Beta-cell dysfunction and glucose intolerance: results from the San Antonio metabolism (SAM) study. *Diabetologia.* 47:31-39.

Giaccari, A., Sorice, G. and Muscogiuri, G. (2009). Glucose toxicity: The leading actor in the pathogenesis and clinical history of type 2 diabetes - mechanisms and potentials for treatment. *Nutrition, Metabolism and Cardiovascular Diseases*. 19:365-377.

Gomes, A., Vedasiromoni, J.R., Das, M., Sharma, R.M. and Ganguly, D.K. (2001). Antihyperglycemic effect of black tea (Camellia sinensis) in rat. *Journal of Ethnopharmacology*. 27: 243±275.

*UD$0 DQG)ODWW 35 1DWXUH¶V RZQ SKDUPDF\WK e diabetes perspective. *Proceedings of the Nutrition Society*. 56: 507-517.

Grill, V. and Björklund, A. (2009). Impact of metabolic abnormalities for beta cell function: Clinical significance and underlying mechanisms. *Molecular and Cellular Endocrinology*. 297:86-92.

Gross, B. and Staels, B. (2007). PPAR agonists: multimodal drugs for the treatment of type-2 diabetes. *Best Practice and Research Clinical Endocrinology and Metabolism.* 21(4):687-710.

Grover, J.K., Yadav, S., Vats, V., 2002. Medicinal plants of India with anti-diabetic potential. *Journal of Ethnopharmacology.* 81:81-100.

Guerre-Millo, M. (2008). Adipose tissue and adipokines: for better or worse. *Diabetes Metabolism*. 30:13-19.

Gupta, V. K. and Sharma, S. K. (2006). Plants as natural antioxidants. *Natural Product Radiance.* 5(4):326-334.

Hajer, G.R., Van Haeften, T.W., Visseren, F.L.J. (2008). Adipose tissue dysfunction in obesity, diabetes and vascular diseases. *European Heart Journal*. 29:2959-2971.

Hardie, D.G. (2004). The AMP-activated protein kinase pathway: new players upstream and downstream. *Journal Cell Science*. 117:5479-87.

Hardie, D.G. (2007). AMP-activated protein kinase as a drug target. *Annual Review of Pharmacology and Toxicology*. 47:185-210.

Hardie, D.G. (2011). Energy sensing by the AMP-activated protein kinase and its effects on muscle metabolism. *Protocol in Nutrition Society*. 70:92-99.

Harrison, D., Kathy, V., Horing, B. and Drexler, H. (2003). Role of oxidative stress in atherosclerosis. *American Journal of Cardiology*. 91:7-11.

+DVHQDK$+RXJKWRQ3-DQG6RXPDQDWK$. -Amylase inhibitory activity of some Malaysian plants used to treat diabetes; with particular reference to *Phyllanthus amarus*. *Journal of Ethnopharmacology*. 107:449-455.

He, M., Siow, R. C. M., Sugden, D., Gao, L., Cheng, X. and Mann, G. E. (2011). Induction of HO-1 and redox signiling in endothelial cells by advanced glycation

end products: a role for Nrf2 in vascular protection in diabetes. *Nutrition, Metabolism and Cardiovascular Diseases.* 21(4):277-285.

Heim, K. E., Tagliaferro, A. R. and Bobilya, D. J. (2002). Flavonoid antioxidants: chemistry, metabolism and structure-activity relationships. *Journal of Nutritional Biochemistry*. 13: 572-584.

Henke, B.R. and Sparks, S.M.(2006). Glycogen phosphorylase inhibitors. *Mini Review of Medicine Chemistry*. 6:845-857.

Henry, R.R. (2003). Insulin resistance: from predisposing factor to therapeutic target in type 2 diabetes. *Clinical Therapeutics*. Volume 25, supplement B.

Hevener, A. L., Olefsky, J. M., Reichart, D. et al. (2007). Macrophage PPAR gamma is required for normal skeletal muscle and hepatic insulin sensitivity and full antidiabetic effects of thiazolidinediones. *The Journal of Clinical Investigation*. 117:1658-1669.

Hoelz, L. V. B., Horta, B. A. C., Araújo, J. Q., Albuquerque, M. G., de Alencastro, R. B. and da Silva, J. F. M. (2010). Quantitative structure-activity relationships of antioxidant phenolic compounds. *Journal of Chemistry and Pharmacology Research*. 2(5):291-306.

Hu, F.B and Manson, J.E. (2003). Management of diabetes: diet and lifestyle modification. In: Textbook of Diabetes Vol. 1 Ed. John C Pickup & Gareth Williams. pp 36.1-36.13.

Hu F, Rimm E.B., Stampfer M.J., Ascherio A., Spiegelmann D. and Willett W.C. (2000). Prospective study of major dietary patterns and the risk of coronary heart disease in men. *American Journal Clinical Nutrition*. 72:912-921.

Hu, F. B. (2003). Sedentary lifestyle and risk of obesity and type 2 diabetes. *Lipids.* 38(2):103-8.

Huang, T. H. W., Peng, G., Kota, B.P., Li, G. Q., Yamahara, J., Roufogalis, B. D. and Li. Y. (2005). Anti-diabetic action of Punica granatum flower extract: Activation of PPAR and identification of an active component. *Toxicology and Applied Pharmacology*. 207:160-169.

Huang, X. F. and Chen, J.Z. (2009). Obesity, the PI3K/Akt signal pathway and colon cancer. *Obesity Review*. 10: 610-616.

Husen, R., Pihie, A. H. L. and Nallappan, M. (2004). Screening for antihyperglycaemic activity in several local herbs of Malaysia. *Journal of Ethnopharmacology*. 95:205-208.

Hussain, A., Claussen, B., Ramachandran, A. and Williams, R. (2007). Prevention of type 2 diabetes. *Diabetes Research and Clinical Practice*, 76:317-326.

Huxley, R.R. and Neil, H. (2003). The relationship between dietary flavonol intake and coronary heart disease mortality: a meta analysis of prospective cohort studies. *European Journal of Clinical Nutrition.* 57:904-908.

Ibuka, A.S., Morita, Y., Terada, T., Asakura, T., Nakajima, K., Iwata, S., Misaka, T., Sorimachi, H., Arai, S., and Abe, K. (2006). Crystal Structure of Neoculin: Insights into its Sweetness and Taste-modifying Activity. *Journal Molecular Biology*. 359:148-158.

Institute for Medical Research, (2002) Compendium of Medicinal Plants Used in Malaysia. Kuala Lumpur.

International Diabetes Federation (2012). Web page: http://www.idf.org/latestdiabetes-figures-paint-grim-global-picture (accessed: 2012).

International Trade Centre (2005). Web page: http://www.statistics.gov.my (accessed: 2009).

Iwaki, M., Matsuda, M., Maeda, N., Funahashi, T., Matsuzawa, Y., Makishima, M. and Shimomura, I. (2003). Induction of adiponectin, a fat-derived antidiabetic and antiatherogenic factor, by nuclear receptors. *Diabetes*. 52:1655-1663.

Jantan, I. (2004). Joining the hunt for forest balms. FRIM in Focus. Kuala Lumpur. ISSN.

Jenson, S. D., Robertorye, R. S., Bohling, S. D., Schumacher, J. A., Morgan, J. W., Lim, M. S. and Elentinoba-Johnson, K. S. J. (2003). Quality of starting total RNA is associated with quality of RNA amplified. *Journal of Clinical Pathology*. 56:307-312.

Jia, Q., Liu, X., Wu, X., Wang, R., Hu, X., Li, Y. et al. (2009). Hypoglycemic activity of a polyphenolic oligomer-rich extract of Cinnamomum parthenoxylon bark in normal and streptozotocin-induced diabetic rats. *Phytomedicine*. 16(8):744-750.

Jie, Y., Seong-Il, H. and Myeong-Hyeon, W. (2008). Antioxidant and antidiabetic activities of extracts from *Cirsium japonicum* roots. *Nutrition Research and Practice.* 2(4):247-251.

Joshi, S., Chanotiya, C.S., Agarwal, G., Prakesh, O., Pant, A.K. and Methela, C.S. (2008). Terpenoide compositions and antioxidant and antimicrobial properties of the rhizome essential oil of different Hedychium species. *Chemistry and Biodiversity*. 5:299-309.

Jung, S.H., Seol, H.J., Jeon, S.J., Son, K.H. and Lee, J.R. (2009). Insulin-sensitizing activities of tanshinones, diterpene compounds of the root of *Salvia miltiorrhiza* Bunge. *Phytomedicine*. 16:327–335.

Kadowaki, T. and Yamauchi, T. (2005). Adiponectin and adiponectin receptors. *Endocrine Review*. 26:439-451.

Kant R. (2005). Sweet proteins--potential replacement for artificial low calorie sweeteners. *Nutrition Journal. 9:4-5.*

Kaput, J., Noble, J., Hatipoglu, B., Kohrs, K., Dawson, K. and Bartholomew, A. (2007). Application of nutrigenomic concepts to Type 2 diabetes mellitus. *Nutrition, Metabolism and Cardiovascular Diseases*. 17:89-103.

Kendall, C. W. C., Esfahani, A. and Jenkins, D. J. A. (2010). The link between dietary fibre and human health. *Food Hydrocolloids*. 24:42-48.

Khan, S.E. (2003). The relative contributions of insulin resistance and -cell dysfunction to the pathophysiology of type 2 diabetes. *Diabetologia*. 46:3-19.

Kim, S. P., Ellmerer, M., Van Citters, G. W. and Bergman, R. N. (2003). Primacy of hepatic insulin resistance in the development of the metabolic syndrome induced by an isocaloric moderate-fat diet in the dog. *Diabetes*. 52:2453-2460.

King, K. M. and Rubin, G. (2003). A history of diabetes: from antiquity to discovering insulin. *British Journal of Community Nursing*. 12:1091-1095.

Kontogianni, M. D., Liatis, S., Grammatikou, S., Perrea, D., Katsilambros, N. and Makrilakis, K. (2012). Changes in dietary habits and their association with metabolic markers after a non-intensive, community-based lifestyle intervention to prevent type 2 diabetes, in Greece. The DEPLAN study. *Diabetes Research and Clinical Practice*. 95(2):207-214.

Kowluru, R. A., Abbas, S. N. and Odenbach, S. (2004). Reversal of hyperglycemia and diabetic nephropathy: effect of reinstitution of good metabolic control on oxidative stress in the kidney of diabetic rats. *Journal of Diabetes and its Complications*. 18:282-288.

Krishnaiah,D., Sarbatly, R. and Bono, A. (2007). Phytochemical antioxidants for health and medicine – A move towards nature. Biotechnology and Molecular Biology. 1(4):97-104.

Kumar, N. and Dey, C.S. (2002). Metformin enhances insulin signalling in insulin dependent and-independent pathways in insulin resistant muscle cells. *Journal Pharmacology*. 137: 329–336.

Kuete, V., Krusche, B., Youns, M, Voukeng, I., Fankam, A. G., Tankeo, S., Lacmata, S. and Efferth, T. (2011). Cytotoxicity of some Cameroonian spices and selected medicinal plant extracts. *Journal of Ethnopharmacology*. 134:803-812.

Kurihara,Y and Nirasawa. S. (1994). Sweet, antisweet and sweetness-inducing substances. *Trends in Food Science and Technology*. 51:37-42.

Kuroda, M., Mimaki, Y., Honda, S., Tanaka, H., Yokota, S. and Mae, T (2010). Phenolics from Glycyrrhiza glabra roots and their PPAR- OLJDQG binding activity. *Bioorganic and Medicinal Chemistry*. 18:962-970.

Lafontan, M. and Viguerie, N. (2006). Role of adipokines in the control of energy metabolism: focus on adiponectin. *Current Opinion in Pharmacology*. 6:580-585.

Lalloyer, F., Vandewalle, B., Percevault, F. et al. (2006). Peroxisome proliferator-activated receptor a improves pancreatic adaptation to insulin resistance in obese mice and reduces lipotoxicity in human islets. *Diabetes*. 55:1605-1613.

Langin, D. (2001). Diabetes, insulin secretion, and the pancreatic beta cell mitochondrion. *National England Journal Medicine*. 345:1772-1774.

Lantto T. A., Colucci M., Závadová V., Hiltunen R. and Raasmaja A. (2009). Cytotoxicity of curcumin, resveratrol and plant extracts from basil, juniper, laurel and parsley in SH-SY5Y and CV1-P cells. *Food Chemistry*. 117:405-411.

Laybutt, D. R., Sharma, A., Sgroi, D. C., Gaudet, J., Bonner-Weir, S. and Weir, G. C. (2002). Genetic regulation of metabolic pathways in beta-cells disrupted by hyperglycemia. *Journal Biology Chemistry*. 277:10912-10921.

Leahy, L. J. (2005). Pathogenesis of type 2 diabetes mellitus. *Archives of Madecal Research*. 36:197-209.

Lebovitz, H. E. and Banerji, M. A. (2004). Treatment of insulin resistance in diabetes mellitus. *European Journal of Pharmacology*. 490:135-46.

Lei, Y. C., Hwang, J. S., Chan, C. C., Lee, C. T. and Cheng, T. J. (2005). Enhanced oxidative stress and endothelial dysfunction in streptozotocin-diabetic rats exposed to fine particles. *Environmental Research*. 99:335-343.

Letchuman, G. R., Wan Nazaimoon, W. M., Wan Mohamad, W. B., Chandran, L. R., Tee, G. H., Jamaiyah, H., Isa, M. R., Zanariah, H., Fatanah, I. and Ahmad Faudzi, Y. (2010). Prevalence of diabetes in the Malaysian National Health Morbidity Survey III 2006. *Medical Journal of Malaysia*. 65(3):12-19.

Levin, B. E., Hogan, S. and Sullivan, A. C. (1989). Initiation and perpetuation of obesity and obesity resistance in rats. *American Physiological Society Regulatory, Integrative and Comparative Physiology*. 256:766-771.

Li, R., Wang, W. Q., Zhang, H., Yang, X., Fan, Q., Christopher, T. A., Lopez, B. L., Tao, L.,Goldstein, B. J., Gao, F. and Ma, X. L. (2007). Adiponectin improves endothelial function in hyperlipidemic rats by reducing oxidative/nitrative stress and differential regulation of eNOS/iNOS activity. *American Journal of Physiology, Endocrinology and Metabolism*. 293:1703-1708.

Li, W.L., Zheng, H.C., Bukuru, J. and De Kimpe, N. (2004). Natural medicines used in the traditional Chinese medical system for therapy of diabetes mellitus. *Journal of Ethnopharmacology*. 92(1):1-21.

Li, Y., Wang, P., Zhuang, Y., Lin, H., Li, Y., Liu, L., Meng, Q., Cui, T., Liu, J., Li, Z. (2011). Activation of AMPK by berberine promotes adiponectin multimerization in 3T3-L1 adipocytes. *Federation of European Biochemical Societies Letters*. 585:1735-1740.

Lin, Z., Zhang, Y., Zhang, Y., Shen, H., Hu, L., Jiang, H. and Shen, X. (2008). Oleanolic acid derivative NPLC441 potently stimulates glucose transport in 3 T3-L1 adipocytes via a multitarget mechanism. *Biochemical Pharmacology*. 76:1251-1262.

Liu, S., Sun, J., Yu, L., Zhang, C., Bi, J., Zhu, F., Qu, M. and Yang, Q. (2012). Antioxidant activity and phenolic compounds of Holotrichia parallela motschulsky extracts. *Food Chemistry*. 134:1885-1891.

Liu, Q., Chen, L., Hu, L., Guo, Y. and Shen, X. (2010). Small molecules from natural sources, targeting signaling pathways in diabetes. *Biochimica et Biophysica Acta*. 1799:854-865.

Lombardo, Y. B. and Chicco. A. (2006). Effects of dietary polyunsaturated fatty acids on dislipidemia and insulin resistance in rodents and humans.A review. *Journal of Nutrition Biochemistry*. 17:1-13.

Lu, H., Chen, J., Li, W. L., Ren, B. R., Wu, J. L., Kang, H.Y., Zhang, H. Q., Adams, A., and De Kimpe, N. (2009). Hypoglycemic and hypolipidemic effects of the total triterpene acid fraction from Folium Eriobotryae. *Journal of Ethnopharmacology*. 122:486-491.

Lucas, V. B. H., Bruno, A. C., Horta, J. Q., Magaly, G. A., Ricardo, B. A. and Joaquim, F. M. (2010). Quantitative structure-activity relationships of antioxidant phenolic compounds. *Journal of Chemistry and Pharmacology. Research*. 2(5):291-306.

Maeda, N., Takahashi, M., Funahashi, T., Kihara, S., Nishizawa, H., Kishida, K., Nagaretani, H., Matsuda, M., Komuro, R., Ouchi, N., Kuriyama, H., Hotta, K., Nakamura, T., Shimomura, I. and Matsuzawa, Y. (2001). PPAR- ligands increase expression and plasma concentrations of adiponectin, an adipose-derived protein. *Diabetes.* 50:2094-2099.

Malecki, M. T. (2005). Genetics of type 2 diabetes mellitus. *Diabetes Research and Clinical Practice*. 68:10-21.

Malviya, N., Jain, S. and Malviya, S. (2010). Antidiabetic potential of medicinal plants. *Acta Pol Pharmacology*. 67(2):113-118.

Manach, C., Scalbert, A., Morand, C., Remesy, C., and Jime´nez, L. (2004). Polyphenols: food sources and bioavailability. *American Journal of Clinical Nutrition*. 79:727±747.

Mandard, S., Müller, M. and Kersten, S. (2004). Peroxisome proliferator- activated receptor alpha target genes. *Cell Molecular Life Science*. 61:393-416.

Mariod, A. A., Ibrahim, R. M., Ismail, M. and Ismail, N. (2010). Antioxidant activities of phenolic rich fractions (PRFs) obtained from black mahlab (Monechma ciliatum) and white mahlab (*Prunus mahaleb*) seedcakes. *Food Chemistry*. 118:120-127.

Marquez-García, B. and Córdoba, F. (2010). Antioxidative system in wild populations of *Erica andevalensis*. *Environmental and Experimental Botany*. 68(1):58-65.

Marshall, J. A. and Bessesen, D. H. (2002). Dietary fat and the development of type 2 diabetes. *Diabetes Care*. 25:620-622.

Martineau, L. C., Couture, A., Spoor, D., Andaloussi, A. B., Harris, C., Meddah, B., Leduc, C., Burt, A., Vuong, T., Le, P. M., Prentki, M., Bennett, S. A., Arnason, J. T. and Haddad, P. S. (2006). Anti-diabetic properties of the Canadian lowbush blueberry *Vaccinium angustifolium Ait*. *Phytomedicine*. 13:612±623.

Masiello, P., (2006). Animal models of type- GLDEHWHV ZLWK UHGXFHG SDQFUHDWLF mass. *The International Journal of Biochemistry and Cell Biology*. 38:873-893.

McCarthy, M. I. (2002). Susceptibility gene discovery for common metabolic and endocrine traits. *Journal Molecular Endocrinology*. 28:1-17.

McCarthy, M. I. and Froguel, P. (2002). Genetic approaches to the molecular understanding of type 2 diabetes. *American Journal Physiology and Endocrinology Metabolism*. 283: 217-225.

McCarthy, M. I. (2010). Genomics, type 2 diabetes, and obesity. *New England Journal Medicine*. 363:2339-2350.

McLaughlin, S. A., Crandall, C. S. and McKinney, P. E. (2001). Octreotide: an antidote for sulfonylurea-induced hypoglycaemia. Annual Emergency Medical. 37:417-418.

Mitchell, S. and Frayling, T. (2002). The role of transcription factors in maturity-onset diabetes of the young. *Molecular Genetic Metabolism*. 77:35-43.

Miyazaki, Y., Pipek, R., Mandarin, L.J. and DeFronzo, R.A. (2003). Tumor necrosis factor alpha and insulin resistance in obese type 2 diabetic patients. *International Journal Obesity Related Metabolic Disorder*. 27:88-94.

Mohd. Firdaus, I, Nur Ashikin Psyquay, A, Ghizan, S. and Maznah, I. (2010). Anthesis and flower visitors in Curculigo latifolia Dryand. *Journal of Biology and Life Sciences***.** 1(1): 13-15.

Monnier, L., Colette, C. and Owens, D.R. (2008). Type 2 diabetes: A well-characterised but suboptimally controlled disease. Can we bridge the divide? *Diabetes and Metabolism*. 34:207±216.

Mythili, M. D., Vyas, R., Akila, G. and Gunasekaran, S. (2004). Effect of streptozotocin on the ultrastructure of rat pancreatic islets. *Microscopy Research and Technique*. 63: 274±281.

Nagappa, A. N., Thakurdesai, P. A., Raob, N. V. and Singh, J. (2003). Antidiabetic activity of *Terminalia catappa Linn* fruits. *Journal of Ethnopharmacology*. 88:45-50.

Nathan, D.M. (2002). Clinical practice. Initial management of glycemia in type 2 diabetes mellitus. *New England Journal of Medicine*. 347:1342-134.

National Diabetes Statistics 2011 (2011). Web page: http://www.cdc.gov/diabetes/pubs/references11.htm (accessed: 2011).

National Institute of Environmental Health Sciences (2001). Guidance Document on Using *In Vitro* Data to Estimate *In Vivo* Starting Doses for Acute Toxicity. NIH Publication No: 01-4500

Noipha, K., Ratanachaiyavong, S. and Ninla-aesong, P. (2010). Enhancement of glucose transport by selected plant foods in muscle cell line L6. *Diabetes Research and Clinical Practice*. 89:22-26.

Nur Akmal, I., Maznah, I., Muhajir, H., Zalinah, A. and Siti Aisyah, A. G. (2013). Antidiabetic and hypolipidemic activities of Curculigo latifolia fruit:root extract in

high fat fed diet and low dose STZ induced diabetic rats. Evidence-based Complementary and Alternative Medicine. http://dx.doi.org/10.1155/2013/601838.

Nzerue C. M., Thomas J., Volcy J. and Edeki T. (2003). Use of octreotide to treat prolonged sulfonylurea-induced hypoglycaemia in a patient with chronic renal failure. *International Journal of Artificial Organs*. 26:86-89.

Okezie, I. A., Vidushi, S. N., Theeshan, B. and Ling-Sun, J. (2007). Free radicals, antioxidants
and diabetes: embryopathy, retinopathy, neuropathy, nephropathy and cardiovascular complications. *Neuroembryol Aging.* 4:117-137.

Okokon, J. E., Antia Bassey, S. and Udobang John, A. (2012). Antidiabetic activities of ethanolic extract and fraction of Anthocleista djalonensis. *Asian Pacific Journal of Tropical Biomedicine.* 1:461-464.

2¶ DKLOO6 Barroso, I. and Wareham, N. J. (2005). Genetic factors in type 2 diabetes. *Science*. 307:370-373.

Oral, E. A., Simha, V., Ruiz, E., Andewelt, A., Premkumar, A., Snell, P., Wagner, A. J., DePaoli, A. M., Reitman, M. L., Taylor, S. I., Gorden, P. and Garg, A. (2002). Leptin replacement therapy for lipodystrophy. *New Engineering Journal Medicine*. 346:570-578.

Ortiz-Andrade, R. R. V., Rodriguez-Lopez, M. L., Garduno-Ramirez, P., Castillo-Espana, S., Estrada-Soto (2005). Anti-diabetic effect t on alloxanized and normoglycemic rats and some pharmacological evaluations of *Tournefortia hartwegiana*. *Journal of Ethnopharmacology.* 101:37-42.

Palsgaard, J., Brown, A. E., Jensen, M., Borup, R., Walker, M. and Meyts, P. D. (2009). Insulin-like growth factor I (IGF-I) is a more potent regulator of gene expression than insulin in primary human myoblasts and myotubes. *Growth Hormone and IGF Research.* 19:168-178.

Paredes-López, O., Cervantes-Ceja, M. L., Vigna-Pérez, M. and Hérnandez-Pérez, T. (2010). Berries: improving human health and healthy aging, and promoting quality. *Plant Foods for Human Nutrition*. 65:299-308.

Pareek, H., Sharma, S., Khajja, B. S., Jain, K. and Jain, G. C. (2009). Evaluation of hypoglycemic and anti hyperglycemic potential of Tridax procumbens (Linn.). *BMC Complement and Alternative Medicine.* 9:48-56.

Park, M. Y., Lee, K., S. and Sung, M. K. (2005). Effect of dietary mulberry, Korean red JLQVHQJ DQG EDQDQD RQ JOXFRVH KRPHRVWDVLV LQ UHODWLRQ WR 33$5. 33$5 LPL mRNA expressions. *Life Sciences*. 77(26): 3344-3354.

Patel, D.K., Kumar, R., Laloo, D. and Hemalatha, S. (2012). Diabetes mellitus: An overview on its pharmacological aspects and reported medicinal plants having antidiabetic activity. *Asian Pacific Journal of Tropical Biomedcine*. 1:411-420.

Patel, D. K., Kumar, R., Prasad, S. K. and Hemalatha, S. (2011). Pedalium murex Linn (Pedaliaceae) fruits: A comparative antioxidant activity of its different fractions. *Asian Pacific Journal of Tropical Biomedicine*. 1:395-400.

Patsouris, D., Müller, M. and Kersten, S. (2004). Peroxisome proliferators activated receptor ligands for the treatment of insulin resistance. *Current Opinnion Investigation Drugs*. 5: 1045-1050.

Patwardhan, B. (2005). Ethnopharmacology and drug discovery. *Journal of Ethnopharmacology*. 100:50-52.

Perseghin, G., Caumo, A., Arcelloni, C., Benedini, S., Lanzi, R., Pagliato, E., ereni, L. P., Testolin, G., Battezzati, A., Comi, G., Comola, M. and Luzi, L. (2003). Contribution of abnormal insulin secretion and insulin resistance to the pathogenesis of type 2 diabetes in myotonic dystrophy. *Diabetes Care*. 26:2112-2118.

Petersen, K. F., Oral, E. A., Dufour, S., Befroy, D., Ariyan, C., Yu, C., Cline, G. W., DePaoli, A. M., Taylor, S. I., Gorden, P. and Shulman, G. I. (2002). Leptin reverses insulin resistance and hepatic steatosis in patients with severe lipodystrophy. *Journal Clinical Investigation*. 109:1345±1350.

Petersen, K. F. and Shulman, G. I. (2002). Pathogenesis of skeletal muscle insulin resistance in type 2 diabetes mellitus. *American Journal Cardiology*. 90:11-18.

Petersson, U., Östgren, C. J., Brudin, L., Brismar, K. and Nilsson, P. M. (2009). Low levels of insulin-like growth-factor-binding protein-1 (IGFBP-1) are prospectively associated with the incidence of type 2 diabetes and impaired glucose tolerance (IGT): The Söderåkra Cardiovascular Risk Factor Study. *Diabetes and Metabolism*. 35:198±205.

Phielix, E. and Mensink, M. (2008). Type 2 Diabetes Mellitus and Skeletal Muscle Metabolic Function. Physiology and Behavior. 94:252-258.

Phillips, C. M., Tierney, A. C. and Roche, H. M. (2008) Gene±nutrient interactions in the metabolic syndrome. *Journal of Nutrigenetics and Nutrigenomics*. 1:136-151.

Pietta, P. G. (2000). Flavonoids as antioxidants. *Journal of Natural Products*. 63:1035-1042.

Pita, J., Panadero, A., Soriano-Guillén, L., Rodríguez, E. and Rovira, A. (2012). The insulin sensitizing effects of PPAR- DJRQLVW DUH DVVRFLDWHG WR FKDQJHV L adiponectin index and adiponectin receptors in Zucker fatty rats. *Regulatory Peptides*. 174:18-25.

Poitout V. and Robertson R. P. (2002). Minireview : Secondary beta-cell failure in type 2 diabetes mellitus-a convergence of glucotoxicity and lipotoxicity. *Endocrinology*. 143: 339-342.

Ponnusamy, S., Ravindran, R., Zinjarde, S., Bhargava, S., Kumar, A.R. (2011). Evaluation of traditional Indian antidiabetic medicinal plants for human pancreatic amylase inhibitory effect in vitro. *Evidence Based Complement Alternative Medicine*. 2:515-647.

Poulose, N., Vishnu Prasad, C. N., Nidhina Haridas, P. A. and Anilkumar, G. (2011). Ellagic acid stimulates glucose transport in adipocytes and muscles through AMPK mediated pathway. *Journal of Diabetes and Metabolism*. 2:7-11.

Pounis, G.D., Tyrovolas, S., Antonopoulou, M., Zeimbekis, A., Anastasiou, F., Bountztiouka, V., Metallinos, G., Gotsis, E., Lioliou, E., Polychronopoulos, E., Lionis, C. and Panagiotakos, D.B. (2010). Long-term animal-protein consumption is associated with an increased prevalence of diabetes among the elderly: The Mediterranean islands (MEDIS) study. *Diabetes and Metabolism*. 36:484-490.

Prasad, D. S., Kabir, Z., Dash, A. K. and Das, B. C. (2011). Abdominal obesity, an independent cardiovascular risk factor in Indian subcontinent: a clinico epidemiological evidence summary. *Journal of Cardiovascular Disease Research*. 2:199-205.

Prasad, D. S., Kabir, Z., Dash, A. K. and Das, B. C. (2012). Prevalence and risk factors for diabetes and impaired glucose tolerance in Asian Indians: A community survey from urban Eastern India. *Diabetes and Metabolic Syndrome: Clinical Research and Reviews.* 2(1):155-160.

Prasad, D. S., Kabir, Z., Dash, A. K. and Das, B. C. (2010). Cardiovascular risk factors in developing countries: a review of clinico-epidemiological evidence. *CVD Prevention and Control*. 5:115-23.

Prentki, M., Joly, E., El-Assaad, W. and Roduit, R. (2002). Malonyl-CoA signaling, lipid partitioning, and glucolipotoxicity: role in beta-cell adaptation and failure in the etiology of diabetes. *Diabetes*. 51:405-413.

Radziuk, J. and Pye, S. (2002). Quantitation of basal endogenous glucose production in type II diabetes. Importance of the volume of distribution. *Diabetologia*. 45:1053-84.

Rakatzi, I., Stosik, M., Gromke, T., Siddle,K. and Eckel, J. (2006). Differential phosphorylation of IRS-1 and IRS-2 by insulin and IGF-I receptors. *Archives of Physiology and Biochemistry.* 112:37-47.

Rakhshandehroo, M., Knoch, B., Muller, M. and Kersten, S. (2010). Peroxisome proliferator activated receptor alpha target genes. *PPAR Research*. 12(2):132-138.

Raghavan, S., Kristinsson, H. G., and Leeuwenburgh, C. (2008). Radical scavenging and reducing ability of tilapia (Oreochromis niloticus) protein hydrolysates. *Journal of Agricultural and Food Chemistry*. 56(21):10359-10367.

Randhir, R. and Shetty, K. (2007). Mung beans processed by solid-state bioconversion improves phenolic content and functionality relevant for diabetes and ulcer management. *Innovative Food Science and Emerging Technologies.* 8(2):197-204.

Rangachari, B. and Savarimuthu, I. (2011). Antidiabetic and Hypolipidemic effect of methanol extract of *Lippia nodiflora* L. in streptozotocin induced diabetic rats. *Asian Pacific Journal of Tropical Biomedicine*. 1(1): 30-36.

Raptis, A. E. and Viberti, G. (2001). Pathogenesis of diabetic nephropathy. *Experiment Clinical Endocrinology Diabetes*. 109:424-437.

Ravnskjaer, K., Boergesen, M., Rubi, B. et al. (2005). Peroxisome proliferator-activated receptor a (PPARa) potentiates, whereas PPARg attenuates, glucose-stimulated insulin secretion in pancreatic b-cells. *Endocrinology*. 146:3266-3276.

Rawat, S., Bhatt, I. D. and Rawal, R. S. (2011). Total phenolic compounds and antioxidant potential of Hedychium spicatum Buch. Ham. ex D. Don in west Himalaya, India. *Journal of Food Composition and Analysis.* 24:574-579.

Reed, M. J., Meszaros, K., Entes, L. J., Claypool, M. D., Pinkett, J. G., Gadbois, T. M. and Reaven, G. M. (2000). A New Rat Model of Type 2 Diabetes: The Fat-Fed, Streptozotocin-Treated Rat. *Metabolism*. 49:1390-1394.

Rees, D. A. and Alcolado, J. C. (2005). Animal models of diabetes mellitus. *Diabetic Medicine*. 22:359-370.

Reis, M., Lobato, B.. Lameira, J., Santos, A. S. and Alves, C. N. (2007). A theoretical study of phenolic compounds with antioxidant properties. *European Journal of Medical Chemistry.* 42:440-446.

Reuter, T. Y. (2007). Diet-induced models for obesity and type 2 diabetes. *Drug Discovery Today : Disease Models*. 191.

Renwick, A.G. (2006). The intake of intense sweeteners-An updated review. *Food Additive and Contamination*. 23(4):327-338.

Rhodes, C. J. and White, M. F. (2002). Molecular insights into insulin action and secretion. *European Journal of Clinical Investigation*. 32(3):3-13.

Risérus, U., Willett, W.C. and Hu, F.B. (2009). Dietary fats and prevention of type 2 diabetes. *Progress in Lipid Research*. 48:44-51.

Rizzo, M., Kotur-Stevuljevic, J., Berneis, K., Spinas, G., Rini, G. B., Jelic-Ivanovic, Z., Spasojevic-Kalimanovska, V. and Vekic, J. (2009). Atherogenic dyslipidemia and oxidative stress:a new look. *Translational Research*. 153:217±223.

Robertson, R. P. (2004). Chronic oxidative stress as a central mechanism for glucose toxicity in pancreatic islet beta cells in diabetes. *Journal Biology Chemistry*. 279:42351-42354.

Robertson, R. P. and Harmon, J. S. (2006). Diabetes, glucose toxicity, and oxidative stress: A case of double jeopardy fRU WKH SDQFUHDWLF LVOHW *Free Radical Biology and Medicine.* 41:177-184.

Robertson, R.P., Harmon, J., Tran, P.O. and Poitout, V. (2004). Beta-cell glucose toxicity, lipotoxicity, and chronic oxidative stress in type 2 diabetes. *Diabetes*. 53: 119±124.

Roden, M. and Bernroider, E. (2003). Hepatic glucose metabolism in humans ± its role in health and disease. *Best Practice and Research Clinical Endocrinology and Metabolism.* 17(3): 365-383.

Roffey, B. W. C., Atwal, A. S., Johns, T. and Kubow, S. (2007). Water extracts from *Momordica charantia* increase glucose uptake and adiponectin secretion in 3T3-L1 adipose cells. *Journal of Ethnopharmacology*. 14:34-39.

Rossi, A. S., Lombardo, Y. B. and Chicco, A. G. (2010). Lipogenic enzyme activities and glucose uptake in fat tissue of dyslipemic, insulin-resistant rats: Effects of fish oil. *Nutrition*. 26: 209-217.

Rumbaoa, R. G., Malviya N, Jain S. and Malviya S. (2010). Antidiabetic potential of medicinal
plants. *Acta and Policy of Pharmacology*. 67(2):113-118.

Sahin, K., Onderci, M., Tuzcu, M. et al., (2007). Effect of chromium on carbohydrate and lipid metabolism in a rat model of type 2 diabetes mellitus: the fat-fed, streptozotocin-treated rat. *Metabolism*. 56(9):1233-1240.

Samee, W., Nunthanavanit, P. and Ungwitayatorn, J. (2008). 3D-QSAR Investigation of Synthetic Antioxidant Chromone Derivatives by Molecular Field Analysis. *International Journal of Molecular Science.* 9(3):235-246.

Sancho, R. A. S. and Pastore, G. M. (2012). Evaluation of the effects of anthocyanins in type 2 diabetes. *Food Research International.* 46:378-386.

Sanz, C., Gautier, J. F. and Hanaire, H. (2010). Physical exercise for the prevention and treatment of type 2 diabetes.*Diabetes and Metabolism*. 36:346-351.

Sawant, S. P., Dnyanmote, A. V. and Mehendale, H. M. (2007). Mechanisms of inhibited liver tissue repair in toxicant challenged type 2 diabetic rats. *Toxicology*. 232:200-215.

Schenk, S., Cook, J. N., Kaufman, A. E. and Horowitz, J. F. (2005). Postexercise insulin sensitivity is not impaired after an overnight lipid infusion. *American Journal Physiology Endocrinology Metabolism*. 288:519-525.

Schenk, S. and Horowitz, J. F. (2007). Acute exercise increases triglyceride synthesis in skeletal muscle and prevents fatty acid-induced insulin resistance. *Journal Clinical Investigation*. 17:1690-1698.

Schrauwen, P. and Hesselink, M. K. (2004). Oxidative capacity, lipotoxicity, and mitochondrial damage in type 2 diabetes. *Diabetes.* 53:1412-1417.

Seeram, N. P. and Nair, M. G. (2002). Inhibition of lipid peroxidation and structure± activity related studies of the dietary constituents anthocyanins, anthocyanidins, and catechins. *Journal of Agricultural and Food Chemistry*. 50:5308-5312.

Seidell, J. C. (2000). Obesity, insulin resistance and diabetes - a worldwide epidemic. *British Journal of Nutrition.* 83(1):5-8.

Shafrir, E. (2003). Diabetes in animals: Contribution to the understanding of diabetes by study of its etiophatology in animal models. In: Porte, D., Sherwin, R. S. and Baron, A editors. Diabetes mellitus. New York: McGraw-Hill: 231-255.

Sheng, T. and Yang, K. (2008). Adiponectin and its association with insulin resistance and type 2 diabetes. *Journal of Genetics and Genomics*. 35:321-326.

Sheng, H. and Sun, H. (2011). Synthesis, biology and clinical significance of pentacyclic triterpenes: a multi-target approach to prevention and treatment of metabolic and vascular diseases. *Natural Product Report*. 28:543-593.

Shingo, A. S., Kanabayashi, T., Murasea, T. and Kito, S. (2012). Cognitive decline in STZ-3V rats is largely due to dysfunctional insulin signaling through the dentate gyrus. *Behavioural Brain Research*. 229:378-383.

Shirasuka, Y., Nakajima, K., Asakura, T., Yamashita, H., Yamamoto, A. and Hata, S. (2004). Neoculin as a new taste-modifying protein occurring in the fruit of *Curculigo latifolia*. *Bioscience Biotechnology Biochemical*. 68:1403-1407.

Shukla, R., Sharma, S. B., Puri, D., Prabhu, K. M. and Murthy, P. S. (2000). Medicinal plants for treatment of diabetes mellitus. *Indian Journal of Clinical Biochemistry*. 15:169-180.

Shulman, G. I. (2000). Cellular mechanisms of insulin resistance. *Journal Clinical Investigation.*106:171-176.

Sicree, R., Shaw, J. and Zimmet, P. (2006). Prevalence and projections. In: Gan D, Diabetes atlas, 3rd ed. *Brussels: International Diabetes Federation*. p 16-104.

Sinclair, A. J., Gadsby, R., Penfold, S., Croxon, S. C. M. and Bayer, A. J. (2001). Prevalence of diabetes in care home residents. *Diabetes Care*. 24:1066-1068.

Singh, S. K., Kesari, A. N., Gupta, R. K., Jaiswal, D. and Watal, G. (2007). Assessment of antidiabetic potential of *Cynodon dactylon* extract in streptozotocin diabetic rats. *Journal of Ethnopharmacology*. 114:174-179.

Sirtori, C. R., Galli, C., Anderson, J. W. and Arnoldi, A. (2009). Nutritional and nutraceutical approaches to dyslipidemia and atherosclerosis prevention: Focus on dietary proteins. *Atherosclerosis.* 203:8-17.

Skelin, M., Rupnik, M. and Cencic, A. (2010). Pancreatic beta cell lines and their applications in diabetes mellitus research. *Alternatives to Animal Experiments*. 27:2-10.

Soman, G., Yang, X., Jiang, H., Giardina, S., Vyas, V., Mitra, G., Yovandich, J., Creekmore, S. P., Waldmann, T. A., Quiñones, O. and Alvord, W. G. (2009). MTS dye based colorimetric CTLL-2 cell proliferation assay for product release and stability monitoring of Interleukin-15: Assay qualification, standardization and statistical analysis. *Journal of Immunological Methods*. 348(1):83-94.

Sparks, L. M., Xie, H., Koza, R. A., Mynatt, R., Hulver, M. W., Bray, G. A. and Smith, S. R. (2005). A High-Fat Diet Coordinately Downregulates Genes Required for Mitochondrial Oxidative Phosphorylation in Skeletal Muscle. *Diabetes*. 54(7):1926-1933.

Spranger, J., Kroke, A., Möhlig, M., Bergmann, M., Ristow, M., Boeing, H., and Pfeiffer, A. (2003) Adiponectin and protection against type 2 diabetes mellitus. *Lancet.* 361: 226-228.

Srinivasan, K., Viswanad, B., Asrat, L., Kaul, C.L. and Ramarao, P. (2005). Combination of high-fat diet-fed and low-dose streptozotocin-treated rat: A model for type 2 diabetes and pharmacological screening. *Pharmacological Research*. 52:313-320.

Staels, B. and Fruchart, J. (2005).Therapeutic roles of peroxisome proliferator-activated receptor agonists. *Diabetes*. 54:2460-2470.

Steinberger, J. and Daniels, S. R. (2003). Obesity, Insulin Resistance, Diabetes, and Cardiovascular Risk in Children. *Circulation American Heart Association*. 107:1448-1453.

Steppan, C.M., Bailey, S.T., Bhat, S., Brown, E.J., Banerjee, R.R., Wright, C.M., Patel, H.R., Ahima, R.S., and Lazar, M.A. (2001). The hormone resistin links obesity to diabetes. *Nature*. 409:307-312.

Stoeckli, R. and Keller, U. (2004). Nutritional fats and the risk of type 2 diabetes and cancer. *Physiology and Behavior*. 83:611-615.

Sugano, M., Yamato, H., Hayashi, T., Ochiai, H., Kakuchi, J., Goto, S., Nishijima, F., Iino, N., Kazama, J. J., Takeuchi, T., Mokuda, O., Ishikawa, T. and Okazaki, R. (2006). High-fat diet in low-dose-streptozotocin-treated heminephrectomized rats induces all features of human type 2 diabetic nephropathy: A new rat model of diabetic nephropathy. *Nutrition, Metabolism and Cardiovascular Diseases*. 16:477-484.

Sunil, C., Duraipandiyan, V., Agastian, P. and Ignacimuthu, S. (2012).Antidiabetic effect of plumbagin isolated from *Plumbago zeylanica* L. root and and its effect on GLUT4 translocation in streptozotocin-induced diabetic rats. *Food and Chemical Toxicology*. 50(12):4356-4363.

Suzuki, M., Kurimoto, E., Nirasawa, S., Masuda, Y., Hori, K. and Kurihara, Y. (2004). Recombinant curculin heterodimer exhibits taste-modifying and sweet-tasting activities. *FEBS Letters*. 573:135-138.

Sydow, K. and Münzel, T. (2003). Diabetes mellitus, oxidative stress and endothelial dysfunction. *International Congress Series*. 1253:125-138.

6]XGHOVNL77KHPHFKDQLVPRIDOOR[DQDQGVWUHSWR]RWRFLQDFWLRQLQFHOOVRI rat pancreas. *Physiology Research.* 50:536-546.

Taylor, A. (2006). The genetics of type 2 diabetes: A review. *International Journal Diabetes and Metabolism*. 14:76-81.

Temme, E. H., Van, H. P. G., Schouten, E. G. and Kesteloot, H., (2002). Effect of a plant sterol-enriched spread on serum lipids and lipoproteins in mildly hypercholesterolaemic subjects. *Acta Cardiology*. 57:111-115.

Teppala, S. and Shankar, A. (2010). Association between serum IGF-1 and diabetes among U.S. adults. *Diabetes Care*. 33(10): 2257-2259.

Towler, M. C. and Hardie, D. G. (2007). AMP-activated protein kinase in metabolic control and insulin signaling. *Cirulation Res*earch. 100:328-341.

Trejo-Gutierrez and J.F., Fletcher, G. (2007). Impact of exercise on blood lipids and lipoproteins. *Journal of Clinical Lipidology*. 1:175-181.

Trujillo, E., Davis, C. and Milner, J. (2006). Nutrigenomics, proteomics, metabolomics and the practice of dietetics. *Journal of the American Dietetic Association*. 106(3):403-423.

Turkmen, N., Sari, F. and Sedat Velioglu, Y. (2005). The effect of cooking methods on total phenolics and antioxidant activity of selected green vegetables. *Food Chemistry*. 93(4): 713-718.

Tuomi, T. (2005). Type 1 and Type 2 Diabetes: What Do They Have in Common? *Diabetes*. 54: 40-45

Ulrich, A. B., Schmied, B. M. and Standop, J. (2002). Pancreatic cell lines: a review. *Pancreas*. 24(2):111-120.

Ulrike, A., Carle, F. R. and Kammerer, D. R. (2011). Identification and quantification of phenolic compounds from pomegranate (Punica granatum L.) peel, mesocarp, aril and differently produced juices by HPLC-DAD–ESI/MSn. 127(2):807-821.

Unger, R.H., Clark, G. O, Scherer, P. O. and Orci, L. (2010). Lipid homeostasis, lipotoxicity and the metabolic syndrome. *Biochimica et Biophysica Acta.* 1801:209-214.

Van Dam, R. M., Willett, W. C., Rimm, E. B., Stampfer, M. J. and Hu, F. B. (2002). Dietary fat and meat intake in relation to risk of type 2 diabetes in men. *Diabetes Care*. 25(3):417- 424.

Vasseur, F. (2006). Adiponectin and its receptors: Partners contributing to the "vicious circle" leading to the metabolic syndrome? *Pharmacological Research.* 53:478-481.

Venturini, C. D., Merlo, S., Souto, A. A., Fernandes, M. C., Gomez, R. and Rhoden, C. R. (2010). Resveratrol and red wine function as antioxidants in the nervous

system without cellular proliferative effects during experimental diabetes. *Oxidative Medicine and Cellular Longevity*. 3(6):434-441.

Violleta, B., Mouniera, R., Leclerca, J., Yazigic, A., Foretza, M. and Andreellia, F. (2007). Targeting AMP-activated protein kinase as a novel therapeutic approach for the treatment of metabolic disorders. *Diabetes & Metabolism*. 33:395-402.

Virally, M., Blicklé, J .F., Girard, J., Halimi, S., Simone, D. and Guillausseau. P. J. (2007). Type 2 diabetes mellitus: epidemiology, pathophysiology, unmet needs and therapeutical perspectives. *Diabetes and metabolism*. 33:231-244.

Wang, Y., Zhang, Di., Liu, Y., Yang, Y., Zhao, T., Xu, J. et al. (2009). Association study of the single nucleotide polymorphisms in adiponectin-associated genes with type 2 diabetes in Han Chinese. *Journal of Genetics and Genomics*. 36(7):417-423.

Wang, Y., Yu, J., Zhang, C., Li, P., Zhao, Y., Zhang, M. and Zhou, P. (2012). Influence of flavonoids from Phellinus igniarius on sturgeon caviar: Antioxidant effects and sensory characteristics. *Food Chemistry*. 131:206-210.

Warjeet Singh, L. (2011). Traditional medicinal plants of Manipur as antidiabetics. *Journal of Medicinal Plants Research*. 5:677-687.

Warwick, Z. S., Synowski, S. J., and Bell, K. R. (2002). Dietary fat content affects energy intake and weight gain independent of diet caloric density in rats. *Physiology and Behaviour*. 77:85-90.

Weber, M. B. and Venkat Narayan, K. M. (2008). Preventing type 2 diabetes: Genes or lifestyle? *Primary Care Diabetes.* 2(2):65-66.

Wein, S., Behm, N., Petersen, R.K., Kristiansen, K. and Wolffram, S. (2010). Quercetin enhances adiponectin secretion by a PPAR-LQGHSHQGHQWPHFKDQLVP. *European Journal of Pharmaceutical Sciences*. 41:16-22.

Wheatcroft, S. B. and Kearney, M. T. (2009). IGF-dependent and IGF-independent actions of IGF-binding protein-1 and -2: implications for metabolic homeostasis. *Trends in Endocrinology and Metabolism*. 20(4):212-227.

Wild, S., Roglic, G., Green, A., Sicree, R. and King, G. (2004). Global prevalence of diabetes. Estimates for the year 2000 and projections for 2030. *Diabetes Care.* 27:1047-1052.

Williamson, G. and Manach, C. (2005). Bioavailability and bioefficacy of polyphenols in humans. *American Journal of Clinical Nutrition.* 81:243-255.

Williams, R. J., Spencer, J. P. E. and Rice-Evans, C. (2004). Flavonoids: antioxidants or signaling molecules? *Free Radical Biology and Medicine*. 36(7):838-849.

Wolford, J. K and Vozarova de Courten, B. (2004). Genetic basis of type 2 diabetes mellitus: implications for therapy. *Treat Endocrinology*. 3:257-267.

World Health Organisation. (2006). Defination and diagnosis of diabetes mellitus and intermediate hyperglycemia. Report of a WHO/IDF Consultation.

Wrede, C. E., Dickson, L. M., Lingohr, M. K., Briaud, I. and Rhodes, C. J. (2002). Protein kinase B/Akt prevents fatty acid-induced apoptosis in pancreatic beta-cells (INS-1). *Journal Biology Chemistry*. 277:49676-49684.

Wu, X., Motoshima, H., Mahadev, K., Stalker, T. J., Scalia, R. and Goldstein, B. J. (2003). Involvement of AMP-activated protein kinase in glucose uptake stimulated by the globular domain of adiponectin in primary rat adipocytes. *Diabetes.* 52:1355-1363.

Yamauchi, T., Kamon, J., Ito, Y., Tsuchida, A., Yokomizo, T., Kita, S., Sugiyama, T., Miyagishi, M., Hara, K., Tsunoda, M., Murakami, K., Ohteki, T., Uchida, S., Takekawa, S., Waki, H., Tsuno, NH., Shibata, Y., Terauchi, Y., Froguel, P., Tobe, K., Koyasu, S., Taira, K., Kitamura, T., Shimizu, T., Nagai, R., and Kadowaki, T. (2003). Cloning of adiponectin receptors that mediate antidiabetic metabolic effects. *Nature*. 423:762-769.

Yannick, B., Domitille, S., Feliciano, P., Yohann, C. and Sanchez, J. (2009). Glucotoxicity and pancreatic proteomics. *Journal of Proteomics.* 71(6):576-591.

Yin, J., Hu, R., Chen, M., Tang, J., Li, F., Yang, Y. and Chen, J. (2002). Effects of berberine on glucose metabolism in vitro. *Metabolism,* 51:1439-1443.

Zanariah, H., Chandran, L.R., Wan Mohamad, W.B., Wan Nazaimoon, W.M., Letchuman, G.R., Jamaiyah, H., Fatanah, I., Nurain, M.N., Helen Tee, G.H. and Mohd Rodi, I. (2006). Prevalence of Diabetes Mellitus in Malaysiain 2006 ± Results of the third National health and Morbidity Survey (NHMS III).

Zhang, M., Lv, X., Li, J., Xu, Z. and Chen, L. (2004). The characterization of high-fat diet and multiple low-dose streptozotocin induced type 2 diabetes rat model. *Experimental Diabetes Research*. 9:20-25.

Zhang, Y., Li, X., Zou, D., Liu, W., Yang, J., et al. (2008). Treatment of type 2 diabetes and dyslipidemia with the natural plant alkaloid berberine. *Journal of Clinical Endocrinology and Metabolism*. 93:2559-2565.

Zhang, Z., Liao, L., Moore, J., Wua, T. and Wang, Z. (2009). Antioxidant phenolic compounds from walnut kernels (Juglans regia L.). *Food Chemistry*. 113:160-165.

Zhao, S., Chu, Y., Zhang, C. et al. (2008). Diet-induced central obesity and insulin resistance in rabbits. *Journal of Animal Physiology and Animal Nutrition*. 92(1):105-111.

Zhao, Y. F., Feng, D. D. and Chen, C. (2006). Contribution of adipocyte-derived factors to beta-cell dysfunction in diabetes. *The International Journal of Biochemistry and Cell Biology*. 38:804-819.

Zheng, X. K., Li, Y. J., Zhang, L., Feng, W. S., Zhang, X., (2011). Antihyperglycemic activity of Selaginella tamariscina (Beauv.) Spring. Journal of Ethnopharmacology 133:531-537.

Zheng, X., Zhang, L., Wang,W., Wu, Y., Zhang, Q., Feng, W. (2012). Anti-diabetic activity and potential mechanism of total flavonoids of Selaginella tamariscina (Beauv.) Spring in rats induced by high fat diet and low dose STZ. *Journal of Ethnopharmacology*. 137: 662-668.

Zierath, J. R. (2002). Invited review: exercise training-induced changes in insulin signaling in skeletal muscle. *Journal Application Physiology*. 93:773-781.

Zimmet P., Alberti K.G.M.M. and Shaw T. (2001). Global and social implication of diabetes epidemic. *Nature*. 414: 782-787.

Zimmet, P. (2003). The burden of type 2 diabetes: are we doing enough? D*iabetes Metabolism*. 29: 9-18.

Zimmet, P., Cowie, C., Ekoe, J. M. and Shaw, J. E. (2004). Classification of diabetes mellitus and other categories of glucose intolerance. In: International Textbook of Diabetes Mellitus chapter 1, 3rd Ed., pg 3-14.

Zou, C. and Shao, J. (2008). Role of adipocytokines in obesity-associated insulin resistance. *Journal of Nutritional Biochemistry*. 19:277-286.