
**UNIVERSITI PUTRA MALAYSIA**

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

**NUR AKMAL BINTI ISHAK**

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

**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**

**January 2014**

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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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**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

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**Januari 2014**

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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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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 by Members of Supervisory Committee**

This is to confirm that:

- the research conducted and the writing of this thesis was under our supervision;
- supervision responsibilities as stated in the Universiti Putra Malaysia (Graduate Studies) Rules 2003 (Revision 2012-2013) are adhered to.

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| | |
|---|---|
| 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.

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