UNIVERSITI PUTRA MALAYSIA

ANTIDIABETIC ACTIVITIES OF OIL PALM (Elaeis guineensis Jacq.) FRUIT AND PALM OIL MILL EFFLUENT EXTRACTS

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By

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Diabetes is one of the top ten causes of death in Malaysia. According to the fourth National Health and Morbidity survey conducted in 2011, it is estimated that 15.2% (2.6 million) of Malaysians adults 18 years old and above suffer from diabetes. Most antidiabetic drugs available are associated with several side effects which explain the current prevalence of diabetes. Therefore researches are needed in exploring the new alternative for antidiabetic treatment which are safe, efficient and exert a lesser amount of side effects. Recently the oil palm, *Elaeis guineensis* has been explored in several antidiabetic studies. The oil palm leaves have been found to reduced hyperglycemia in STZ-induced diabetic rats due to the high polyphenolic content. Nevertheless several parts of oil palm which are also contained high amount of polyphenol such as fruit and the effluent from palm oil processing, POME are never been investigated in antidiabetic study. Therefore, this study was conducted to evaluate the antidiabetic properties of oil palm fruit and POME extracts through the *in vivo* antihyperglycemic evaluation. In addition, an initiative was made to study the possible mechanisms involve using *in vitro* models. Raw POME and oil palm fruit were subjected to solvent extraction using ethanol. The extracts collected were further used in the *in vivo* and *in vitro* experiments. To evaluate the antihyperglycemic property of both extracts in diabetic rats, the rats were given the extracts orally using intragastric gavage in the *in vivo* study. The *in vitro* models were design to evaluate the potential antidiabetic mechanisms involve by using the glucose uptake, insulin secretion as well as adiponectin secretion model. The results had shown that acute treatment of POME and oil palm fruit extracts reduced fasting and postprandial hyperglycemia in streptozotocin-induced diabetic rats. Following 28-days treatment, both extracts at concentration of 500 mg kg^{-1} b.w significantly reduced hyperglycemia, improved the body weight and increased insulin secretion in streptozotocin induced diabetes rats. Through *in vitro* evaluation, the oil palm fruit extract (500µg ml^{-1}) were found to stimulate the insulin secretion from BRIN BD11 cell line the most. Moreover both extracts also enhanced basal and insulin mediated glucose uptake into adipocytes, muscles and liver cells. In the evaluation of adiponectin secreting activity, the POME extracts significantly increased adiponectin secretion in both basal and insulin-stimulated state. However the oil palm fruit extracts significantly increased adiponectin secretion only under the insulin stimulated state. The HPLC analysis had shown the presence of gallic acid and

catechin as part of the bioactive compound for both extracts. In conclusion, from *in vivo* evaluation the treatment of POME and oil palm fruit extracts were shown to reduce hyperglycemia at different prandial state in diabetic rats. Both extracts also did not cause severe hypoglycemia in normal rats. The *in vitro* study suggested that the antihyperglycemic property of POME and oil palm fruits were mediated through insulin secretion from pancreatic ß-cells, enhancement of glucose uptake by the muscles, adipocytes and liver cells and amplification of adiponectin secretion from adipocytes cells. Therefore various antihyperglycemic potential of both extracts together with its property that did not cause hypoglycemia make them suitable to be develop as new oral antidiabetic drugs.

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

AKTIVITI ANTIDIABETIS EKSTRAK BUAH KELAPA SAWIT (*Eleais guineensis* Jacq.) DAN SISA EFLUEN KILANG MINYAK SAWIT

Oleh

MOHD FAEZ BIN SHARIF

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Diabetes adalah salah satu penyakit yang berada di tangga teratas yg menyebabkan kematian di Malaysia. Merujuk kepada kaji selidik Kesihatan dan Morbiditi Kebangsaan ke-4 yg dijalankan dalam tahun 2011, dianggarkan sebanyak 15.2% (2.6 juta) penduduk Malaysia dewasa yang berumur 18 tahun dan keatas menghidap penyakit diabetes. Kebanyakan ubat antidiabetik yang terdapat pada masa kini mempunyai kesan sampingan dan ini secara tidak langsung menerangkan tentang fenomena diabetes yang berlaku kini. Oleh itu kajian perlu dilakukan untuk mencari sumber alternatif baru untuk rawatan antidiabetik yang lebih selamat, berkesan dan juga tidak mendatangkan kesan sampingan yang berlebihan. Kini kelapa sawit, *Elais guineensis* telah digunakan dalam beberapa kajian antidiabetik. Daun kelapa sawit telah dibuktikan berjaya menurunkan tahap hyperglisemia tikus aruhan diabetik oleh sebab kandungan polifenol yang tinggi yang terdapat di dalamnya. Walaubagaimanapun kajian masih belum dilakukan terhadap beberapa bahagian lain kelapa sawit yang turut mengandungi kandungan polifenol yang tinggi seperti buah kelapa sawit dan juga sisa dari pemprosesan sawit, POME. Oleh itu kajian ini telah dijalankan untuk menganalisa kesan antidiabetik oleh buah kelapa sawit dan sisa POME melalui penilaian antihiperglisemik secara *in vivo* dan juga untuk mengkaji mekanisma yang mungkin memberi kesan antidiabetik menggunakan model *in vitro.* Sisa POME dan buah kelapa sawit diekstrak menggunakan etanol. Hasil ekstrak seterusnya digunakan di dalam kajian *in vivo* dan *in vitro*. Di dalam kajian *in vivo,* ekstrak diberikan kepada tikus diabetik melalui intragastrik untuk mengkaji sifat antihiperglisemik kedua-dua ekstrak. Model *in vitro* pula direka untuk menghuraikan mekanisma yang mungkin menyebabkan kesan antihiperglisemik menggunakan model pengambilan glukosa, rembesan insulin dan juga model rembesan adiponektin. Keputusan kajian menunjukkan bahawa rawatan secara akut ekstrak sisa POME dan buah kelapa sawit menurunkan hiperglisemia puasa dan posprandial di dalam tikus diabetik aruhan-streptozotocin. Melalui rawatan selama 28 hari, kedua-dua ekstrak pada kepekatan 500 mg kg^{-1} berat badan menunjukkan penurunan hiperglisimea secara signifikan, menambah jumlah berat dan meningkatkan rembesan insulin di dalam tikus diabetik aruhan-streptozotocin. Melalui kajian *in vitro,* ekstrak buah kelapa sawit (500µg ml^{-1}) didapati paling efektif merangsang perembesan insulin dari sel BRIN BD11. Tambahan lagi, kedua-dua ekstrak juga didapati meningkatkan aktiviti pengambilan glukosa basal dan diperantarakan-insulin ke dalam sel-sel adipos, otot dan hati. Melalui kajian rembesan protein

adiponektin, ekstrak sisa POME didapati merangsang perembesan adiponektin di dalam kedua-dua keadaan basal dan juga diperantarakan-insulin. Walaubagaimanapun ekstrak buah kelapa sawit didapati hanya merangsang perembesan adiponektin secara signifikan di dalam keadaan diperantarakan-insulin sahaja. Analisa HPLC menunjukkan kehadiran asid gallic dan catechin sebagai sebahagian daripada bahan bio aktif kedua-dua ekstrak. Sebagai kesimpulan, rawatan ekstrak sisa POME dan buah kelapa sawit didapati menurunkan hiperglisemia di dalam tikus diabetik. Kedua-dua ekstrak juga didapati tidak mengakibatkan kejadian hipoglisemia di dalam tikus normal. Kajian in vitro yang dijalankan menunjukkan bahawa sifat antihiperglisemik ekstrak sisa POME dan buah kelapa sawit tersebut adalah disebabkan oleh rembesan insulin dari sel ß-pankreas, peningkatan dalam pengambilan glukosa ke dalam sel-sel otot, adiposa dan hati dan juga kerana peningkatan rembesan adiponektin dari sel adiposa. Oleh yang demiakan, kepelbagaian potensi antihiperglisemia kedua-dua ekstrak dan juga sifat ekstrak yang tidak mengakibatkan hipoglisemia menjadikan ekstrak-ekstrak tersebut sesuai untuk dibangunkan sebagai ubat antidiabetik yang baru.

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I certify that a Thesis Examination Committee has met on 13th October 2014 to conduct the final examination of Mohd Faez Bin Sharif on his thesis entitle ñAntidiabetic activities of oil palm (*Elaeis guineensis* Jacq.) Fruit and Palm Oil Mill Effluent extractsò 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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LIST OF ABBREVIATIONS

ACUC	Animal Care and Use Committee
$AUC_{Glucose}$	Area under the glucose curve
BGL	Blood glucose level
BSA	Bovine serum albumin
$CaCl_2$	Calcium chloride
DMEM	Dulbeccoôs modified eagleôs medium
DMSO	Dimethylsulfoxide
FBG	Fasting blood glucose
FBS	Fetal bovine serum
FPG	Fasting plasma glucose
HCl	Hydrochloric acid
H_2O	Water
H_2SO_4	Sulfuric acid
HEPES	4-(2-hydroxyethyl)piperazine-1-ethanesulfonic acid
IBMX	3-isobutyl-1-methylxanthine
IDDM	Insulin dependent diabetes mellitus
K^+_{ATP} channel	ATP-sensitive potassium channel
K	Potassium
KCl	Potassium chloride
KRB	Krebs Ringer Bicarbonaate buffer
KH_2PO_4	Potassium dihydrogen phosphate
MgSO4	Magnesium sulphate
MTT	3-(4,5-Dimethyl-2-thiazol)-2,5-diphenyl-2H-tetrazolium Bromide
NaCl	Sodium chloride
$NaHCO_3$	Sodium hydrogen carbonate
NaOH	Sodium hydroxide
NIDDM	Non-insulin dependent diabetes mellitus
OD	Optical density
OPF	Oil palm fruit extract
PBS	Phosphate buffer saline
POME	Palm oil mill effluent
RPMI	Roswell Park Memorial Institute
SDS	Sodium dodecyl sulphate
STZ	Streptozotocin
TNF	Tumor necrosis factor
TZDs	Thiazolidinidiones
TRIS	2-Amino-2-hydroxymethyl-propane-1,3-diol
UPM	Universiti Putra Malaysia
USA	United state of America
WHO	World Health Organization
cm^3	centimeter cubic
µg	microgram
mg	milligram
g	gram
kg	kilogram
µl	microlitre
ml	millilitre

L	Litre
µM	micromolar
mM	millimolar
M	Molar
µm	micrometer
mm	millimeter
m	meter
rpm	round per minute
Ŭ	Alpha
ß	Beta
ɔ	Gamma
%	Percentage
^{o}C	Degree celcius

CHAPTER 1

GENERAL INTRODUCTION

1.1 Background of Study

Diabetes mellitus which characterized by persistent hyperglycemia in blood is a chronic disease that is relatively common throughout the world. It is resulted from defects of insulin secretion or insulin action and can also be cause by combination of both factors (Alberti and Zimmet, 1998). It is normally accompanied by increased risk to oxidative stress, hypertension and severe atherosclerosis (Reusch, 2003)

Diabetes is one of the top ten causes of death in Malaysia. According to the fourth National Health and Morbidity survey conducted in 2011, it is estimated that 15.2% (2.6 million) of Malaysians adults 18 years old and above suffer from diabetes. The amount has bypassed the assumption made by World Health Organization (WHO) which estimated that in the year of 2030, Malaysia would have a total of 2.48 millions diabetes sufferers. This indicates that Malaysia is having a faster increase rate of diabetic disease. The rapid rising trend in the prevalence of diabetes could possibly due to the urbanization, changes in dietary habits, growth of population and inactive lifestyle (Zanariah *et al.,* 2008).

Poor glycemic controls in diabetes patient will always contribute to the prevalence of diabetes complications such as retinopathy, neuropathy, and albuminuria. The records from the Ministry of Health (MOH) showed that the number of diabetic patients admitted to hospitals had increased from 19, 629 cases in 1991 to 30, 661 in 2001. It shows about 56% increments over 10 years. Diabetes mortality rates also increased from 254 death in 1991 to 380 in 2001 (Ooyub *et al.,* 2004). This indicates that diabetes had become major problem in Malaysia. Therefore a stepped up efforts are required in controlling and preventing this chronic disease.

1.2 Statement of Problems

Diabetes can be classified into two class which are type I and type II diabetes mellitus. In type I diabetes, the maintenance of hyperglycemia is limited to insulin therapy (Jacobson *et al.,* 2009). Different types of insulin analogues are available for this purpose such as Humalog, NovoRapid, Levimir and Lantus. Those analogues were categorized according to their times of action onset and duration. On the other hand the regulation of hyperglycemia in type II diabetes patient were mostly by changes of diet, active lifestyle, regular exercise and the uses of oral antidiabetic drugs. Antidiabetic drugs for the treatment of type II diabetes mellitus vary from sulfonylureas, biguanides, thiazolidinediones, r-glucosidase inhibitor, amylin synthetic derivatives and incretin mimetics. The drugs were categorized into different groups based on its antidiabetic mechanisms and mode of action (Chehade and Mooradian, 2000).

The major problem liaises with the conventional antidiabetic drugs were the limitations of the drugs itself. The drugs can bring up undesirable adverse effects such as vomiting, weight gain, nausea and diarrhoea. Furthermore most conventional antidiabetic drugs were also expensive making them unavailable and unaffordable especially in the third world and developing countries where it is difficult to have access to those modern and high cost drugs (Babu *et al.*, 2007). The clinical trial also were still lacking for most antidiabetic drugs making them less efficient (Kirchheiner *et al.,* 2005). For instance, drugs from sulfonylureas group was reported to cause hypoglycemia and weight gain. There are also reports on occurring of death due to prolonged severe hypoglycemia. Metformin on the other hand always associated ZLWK JDVWURLQWHVWLQDO GLVFRPIRUW GLDUUKHD -glucosidase inhibitor also can cause gastrointestinal disturbance, lethal ileus and renal tumors. Meanwhile, drugs from the thiazolidinediones groups can cause fluid retention, liver injury and anemia (Bell, 2002).

Due to the limitations of conventional antidiabetic drugs, searching for a new alternative antidiabetic agent for diabetes treatment is needed. It is crucial to find antidiabetic agents that are safe and efficient to replace the conventional antidiabetic drugs to overcome the limitations brought by those drugs.

1.3 Justification of Study

Palm oil mill effluent (POME) is a waste generated from the oil palm manufacturing process. The POME is often discarded in disposal ponds, resulting in the leaching of contaminants that pollute the groundwater and soil while releasing methane gas to the atmosphere. Tan and colleague reported in 2001 that water soluble phytochemicals from the palm fruit mesocarp which partition into aqueous phase during the oil palm manufacturing process could contains several phenolic compounds. This includes gallic, protocatechuic, gentisic, chlorogenic, coumaric, ferulic, and caffeic acids, as well as hesperidin and catechins (Tan *et al.,* 2001). Recent studies have evaluated the potential of phytochemicals from oil palm in treating various diseases. Oil palm phenolics have been reported previously to inhibit proliferation of estrogen-receptor-positive human breast adenocarcinoma cells, human lung carcinoma cells (Shamala *et al.,* 2010) and promoting vascular relaxation (Mahinda *et al.,* 2002). Furthermore recent study by Rosalina and colleague has revealed the potential of oil palm leaves extract in reducing hyperglycemia and lipid oxidation in STZ-rats (Rosalina *et al.,* 2011). Therefore it is a great effort to evaluate the POME as a new source of oil palm phenolics to treat diabetes. The POME is cheaper and also help reducing environmental pollution as the waste is being utilized.

Phenolic compounds are often found in plants. It comprises of groups such as the phenolic acids, flavonoids and tannins. Several publications on the antioxidative activities of plant derived phenolics have been reported previously (Wang and Ballington, 2007; Materska and Perucka, 2005). Phenolic acids have attracted special attention lately due to its strong inhibitory activity on oxidation induced by peroxyl radicals (Hu and Kitts, 2001). Oil palm fruit is also a rich source of water soluble-phenolics antioxidants like any other fruits. Plants with high phenolics antioxidant

compounds exert high potential as supplements for improving blood glucose control and preventing long-term complications in diabetics (Gallegher *et al.,* 2003). Many research on the antioxidative capacity of the oil palm fruit have been conducted (Neo *et al.,* 2010; Nagendran *et al.,* 2005). Despite the high antioxidant activity of oil palm reported previously however the studies on its potential as alternative antidiabetic agent are never been studied. Therefore this study is conducted to evaluate the potential of oil palm fruit as a new antidiabetic agent to combat diabetes mellitus.

1.4 Hypothesis of Study

I. Treatment of oil palm fruit and POME extracts reduce hyperglycemia in STZ-induced diabetic rats and has no severe hypoglycemia effect in normal rats
II. improve insulin secretion activity of BRIN BD11 cell line
III. improve glucose uptake activity into L6 myotubes, 3T3F442A adipocytes and Chang liver cells and
IV. improve adiponectin secretion activity of 3T3F442A adipocytes.

1.5 Objectives of study

The main objective of this study was to evaluate the antidiabetic properties of oil palm (*Elaeis guineensis*) fruit and POME extract. The specific objectives of this study were:

1. To evaluate the hypoglycaemic and antihyperglycaemic activity of oil palm fruit and POME extracts in normal and STZ-induced diabetic rats.
2. To evaluate the toxicity of oil palm fruit and POME extracts and their effect on adiponectin secretion from adipocyte cells.
3. To investigate the effect of oil palm fruit and POME extract on glucose uptake into muscle, adipocyte and liver cell.
4. To evaluate the effect of oil palm fruit and POME extract on insulin secretion from pancreatic beta cells and to identify the phenolics compound that exists in both extracts.

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