



UNIVERSITI PUTRA MALAYSIA

***EFFECTS OF DABAI (*Canarium odontophyllum* Miq) FRUIT EXTRACT
ON BIOCHEMICAL PARAMETERS OF OBESE DIABETIC RATS***

NURUL NADIRAH BINTI MOKIRAN

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By

NURUL NADIRAH BINTI MOKIRAN

**Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia
in Fulfilment of the Requirements for the Master of Science**

March 2014

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Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment
of the requirement for the degree of Master of Science

**EFFECTS OF DABAI (*Canarium odontophyllum* Miq) FRUIT EXTRACT ON
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March 2013

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Faculty: Medicine and Health Sciences

The number diabetes mellitus incident has exploded globally and elevating over the years. A lot of medications have been extensively introduced to treat the illness. However, synthetic drugs cannot promise the safety upon long term usage. *Dabai* (*Canarium odontophyllum*) is an indigenous fruit of Sarawak that is rich in nutritional value. The main objective of this study was to investigate the effect of *dabai* fruit extract on biochemical parameters of obese-diabetic (Ob-db) rats. At first, the pulp and peel of *dabai* fruit was defatted with petroleum ether and then extracted with 80% of ethanol (v/v). The solvent was then removed and the extract was lyophilized. The *dabai* fruit powder was re-dissolved in 80% of ethanol and its antioxidant capacity was analysed using three different assays; DPPH scavenging activity, β -carotene bleaching assay and oxygen radical absorbance capacity (ORAC) assay. Total phenolic (TPC) and total flavonoid (TFC) contents were measured using spectrophotometer. The phenolic compounds in *dabai* fruit extract were identified by using HPLC-DAD and confirmed by HPLC-ESI-MS. The quantity of identified phenolic compounds in *dabai* fruit extract were in the order of catechin>vanilic acid >apigenin>epicatechin>ferulic acid > ethyl gallate> 4-hydroxybenzoic acid. *In-vivo* study was performed to determine the effect of *dabai* fruit extract on obese-diabetic rats. Male Sprague dawley rats were fed with high-fat diet for three months and followed by the injection of 35 mg streptozotocin (STZ)/kg body weight (BW). *Dabai* extract with doses of 300 and 600 mg/kg BW were supplemented to the rats for 4 weeks. The parameters investigated in this study were glucose level, insulin level, lipid profile [total cholesterol (TC), low density lipoprotein-cholesterol (LDL-c), high density lipoprotein-cholesterol (HDL-c) and triglyceride (TGs)], antioxidant enzymes [glutathione peroxidase (GPx) and superoxide dismutase (SOD)] and endogenous total antioxidant status (TAS). The short term effect of *dabai* fruit extract on glucose level was also evaluated in oral glucose tolerance test (OGTT). The results of this study showed that *dabai* fruit extract with a concentration of 600 mg/kg BW possed the greatest hypoglycemic effect compared to 300 mg/kg BW by significantly reduced glucose level at min 60 to 90 in OGTT accompanied with a

significant reduction in HOMA-IR value. Moreover, the extract (600 mg/kg BW) also showed the greatest improvement in lipid profile by significantly increased HDL-c level and reduced TC and LDL-c level. Other than that, supplementation of 600 mg/kg BW of *dabai* extract also significantly increased GPx level and slightly increased the endogenous total antioxidant status (TAS). However, no effect was observed on TGs and insulin level in both concentrations (300 and 600 mg/kg BW). In conclusion, this study suggests that supplementation of 600 mg/kg BW of *dabai* fruit extract showed anti-diabetic properties and protective effect against its complication by its hypocholesterolaemic properties, short term glucose-lowering effect and improved the insulin resistance and antioxidant status. The bioactive compounds in *dabai* extract might be the one that responsible to improve the disturbance carbohydrate, protein and lipid metabolism in diabetes mellitus.



Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan Ijazah Master Sains

**KESAN EKSTRAK BUAH DABAI (*Canarium odontophyllum* Miq) KE ATAS
PARAMETER-PARAMETER BIOKIMIA TIKUS OBES-DIABETIK**

Oleh

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Bilangan kejadian diabetes mellitus telah melonjak di serata dunia dan meningkat dari tahun ke tahun. Banyak ubat-ubatan telah diperkenalkan dengan meluasnya untuk mengubati penyakit tersebut. Walaubagaimanapun, ubat-ubatan sintetik tidak boleh menjanjikan keselamatan terhadap penggunaannya dalam jangka masa yang panjang. Dabai (*Canarium odontophyllum*) adalah buah tempatan di Sarawak yang kaya dengan nilai zat pemakanan. Objektif utama kajian ini adalah untuk mengkaji kesan buah dabai ke atas parameter-parameter biokimia tikus obes-diabetik. Pada mulanya, lemak pada bahagian isi dan kulit buah dabai telah disingkirkan menggunakan petroleum ether dan kemudian diekstrak menggunakan 80% ethanol (v/v). Kemudian, larutan tersebut disingkirkan dan ekstrak tersebut diliofilisasikan. Serbuk ekstrak dabai telah di larutkan semula di dalam 80% ethanol dan kapasiti antioksidannya telah dianalisa menggunakan tiga assai yang berbeza; aktiviti perencatan radikal bebas DPPH, assai pelunturan β -karoten dan assai kapasiti penyerapan radikal oksigen (ORAC). Jumlah kandungan fenolik (TPC) dan flavon (TFC) telah di ukur menggunakan spektrofotometer. Kompoun fenolik di dalam ekstrak buah dabai telah dikenalpasti menggunakan HPLC-DAD dan dipastikan dengan HPLC-ESI-MS. Kuantiti kompoun fenolik yang dikenalpasti di dalam ekstrak buah dabai adalah dalam susunan catechin > asid vanilik > apigenin > epicatechin > asid ferulik > etil gallate > asid 4-hydrobenzoik. Kajian *in-vivo* telah dijalankan untuk menentukan kesan ekstrak buah dabai ke atas tikus obes-diabetik. Tikus Sprague dawley jantan telah diberi makan dengan diet tinggi lemak selama tiga bulan dan diikuti dengan suntikan 35 mg streptozotocin (STZ)/kg berat badan (BW). Ekstrak dabai dengan dos 300 dan 600 mg/kg BW telah dibekalkan kepada tikus selama 4 minggu. Parameter-parameter yang dikaji di dalam kajian ini adalah paras gula, paras insulin, profil lipid [jumlah kolesterol (TC), lipoprotein ketumpatan rendah-kolesterol (LDL-c), lipoprotein ketumpatan tinggi-kolesterol (HDL-c) dan trigliserida (TGs)], enzim-enzim antioksidan [glutathione peroksida (GPx) dan

superoksida dismutase (SOD)] dan jumlah status antioksidan (TAS). Kesan jangka masa pendek ekstrak buah dabai ke atas paras gula juga di kaji di dalam ujian tolerasi gula (OGTT). Keputusan keseluruhan bagi kajian ini menunjukkan ekstrak buah dabai dengan kepekatan 600 mg/ kg BW mempunyai kesan hipoglisemik yang terbaik berbanding 300 mg/kg BW menurunkan paras glukosa pada min 60 hingga 90 dengan signifikan dalam OGTT diiringi dengan penurunan HOMA-IR yang signifikan. Tambahan pula, ekstrak (600 mg/kg BW) tersebut juga menunjukkan penambahbaikan yang tertinggi di dalam profil lipid dengan meningkatkan paras HDL-c dan menurunkan paras TC dan LDL-c secara signifikan. Selain itu, pembekalan 600 mg/kg BW ekstrak dabai juga meningkatkan paras GPx secara signifikan dan meningkatkan sedikit jumlah status antioksidan (TAS) endogenus. Walaubagaimanapun, tiada kesan yang dilihat ke atas TGs dan paras insulin di dalam kedua-dua kepekatan (300 dan 600 mg/kg BW). Kesimpulannya, kajian ini mencadangkan bahawa pembekalan 600 mg/kg ekstrak buah dabai menunjukkan ciri-ciri antidiabetik dan kesan perlindungan terhadap komplikasinya dengan ciri-ciri hipokolesterol, kesan penurunan gula dalam jangka masa pendek dan menambahbaik insulin rentang dan status antioksida. Kompoun bio-aktif di dalam ekstrak dabai berkemungkinan bertanggungjawab memperbaiki gangguan metabolisme karbohidrat, protein dan lipid dalam diabetes mellitus.

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This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Master of Science. The members of the Supervisory Committee were as follows:

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LIST OF ABBREVIATIONS / ANNOTATIONS

AAPH	2,2'-azobis(2-methylpropionamidine) dihydrochloride
ABTS	2,2'-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid)
ACUC	Animal Care and Use Committee
ADP	Adenosine diphosphate
AGEs	Glycation end-products
ANOVA	Analysis of variance
apoA-1	Apolipoprotein A-1
ATP	Adenosine triphosphate
AUC	Area under curve
BHT	Butylated hydroxytoluene
BMI	Body mass index
BW	Body weight
CVD	Cardiovascular disease
DAD	Diode array detector
DPPH	2,2-diphenyl-1-picrylhydrazyl
DPP-IV	dipeptidyl peptidase IV
EDTA	Ethylenediaminetetraacetic acid
ESI	Electron spray ionization
ESRD	End-stage renal disease
GAE	Gallic acid equivalent
GDM	Gestational diabetes mellitus
GLP-1	glucagon-like peptide-1
GLUT4	glucose transporter type 4
GR	Glutathione Reductase
GPx	Glutathione peroxidase
GSH	Glutathione
GSSG	Oxidised glutathione
H ⁺	Hydrogen
H ₂ O	Water
HCl	Hydrochloric acid
HDL	High-density lipoprotein
HLA	Human leukocyte antigen
HPLC	High-performance liquid chromatography
H ₂ O ₂	Hydrogen peroxide
HOMA-IR	Homeostatic model assessment of Insulin resistance
IC ₅₀	Inhibition concentration to scavenge 50% of radical
IDDM	Insulin-dependent diabetes mellitus
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
LDL	Low-density lipoprotein
LPC	Lysophosphatidylcholine
LPL	Lipoprotein lipase
Mg ²⁺	Magnesium
MW	Molecular weight
NaCl	Sodium chloride
NADPH	Reduced nicotinamide adenine dinucleotide phosphate
NHMS	National Health Morbidity Survey
NIDDM	Non-insulin dependant diabetes mellitus

NEFAs	Non-esterified fatty acids
NO	Nitric oxide
O ₂	Oxygen
OGTT	Oral glucose tolerance test
ORAC	Oxygen radical absorbance capacity
PC	Phosphatidylcholine
PPAR	Peroxisome proliferator-activated receptor
pPLA2	Phospholipase A2
ROS	Reactive oxygen species
SD	Standard deviation
SEM	Standard error of means
SOD	Superoxide dismutase
SPSS	Statistic package for social sciences
STZ	Streptozotocin
Su's	Sulfonylureas
TAS	Total antioxidant status
TMB	3,3',5,5'-tetramethylbenzidine
T1DM	Type-1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TNF	Tumor necrosis factor
t _R	Retention time
Tzd's	Thiazolidinediones
UCP	Uncoupling proteins
UK	United Kingdom
UV	Ultraviolet
Vis	Visible
WHO	World Health Organization

CHAPTER 1

INTRODUCTION

1.1 Research Background

Nowadays, non-communicable diseases are ranked as one of the global top leading causes of death and the prevalence is getting higher from year to year (WHO, 2002). In 2008, 57 million people died all over the world from ten major fatal causes which is ischemic heart disease (12.8%), stroke and cerebrovascular disease (10.8%), lower respiratory infections (6.1%), chronic obstructive pulmonary disease (5.8%), diarrhoeal diseases (4.3%), HIV or AIDS (3.1%), cancer (2.4%), tuberculosis (2.4%), diabetes mellitus (2.2%) and road traffic accidents (2.1%). Out of this number, 36 million of the death (63%) was caused by non-communicable diseases alone with the priority comprised of cardiovascular disease, diabetes mellitus, cancer and chronic lung diseases (WHO, 2011).

Fruits and vegetables are enriched not only with nutrient, multivitamins and minerals, but also contain various bioactive compounds which are worthwhile and favourable to health and diseases (Nestle, 1999). Consumption of both fruits and vegetables have been associated with the prevention and improvement of conditions of several diseases such as cancer, cardiovascular disease, obesity, hypertension and others (Bazzano et al., 2003; Riboli et al., 2003). Moreover, low consumption of fruits and vegetables are identified as one of the risk factor that contributes to higher global burden of diseases (Ezzati et al., 2002). In certain countries, fruits and vegetables are used as complementary or alternative medicine (CAM) to fight certain diseases. Antioxidant compounds such as vitamin C, vitamin E, polyphenol compounds and flavonoids found in fruits and vegetables emerged as one of the determinants in plants speciality because of its unique properties as antioxidant.

Polyphenols refer to any compound that contains phenol structural unit which can be naturally found in plants. Generally, up to 8000 phenolic compounds was identified in diverse plant kingdom and probably thousands more are still not being identified yet. The extensive availability of these compounds in plants including fruits, vegetables and herbs is an indication of indirect daily consumption of polyphenols by humans. Polyphenol compounds are also known as antioxidants because of its free radical scavenging activity which acts as preventive agents against lipid peroxidation and cell destruction. The compounds are associated with antibacterial, anti-inflammatory, antithrombotic, anticarcinogenic and antiallergenic activity, thus making them as one of

the agents responsible in the protection of various chronic diseases (Middleton et al., 2000).

1.2 Statements of Problem

Diabetes mellitus is a chronic non-communicable disease that receives a major concern globally because it causes millions of death every year. In 2008, 1.3 million of people died globally with the highest occurrence resided in the upper and middle income countries (WHO, 2008). In Malaysia, 3 million people was diagnosed with diabetes in 2011, where the number has increased about 5% in just 5 years, which was from 11.6% in 2006 (NHMS III, 2006) to 15.2% in 2011 (NHMS, 2011). In addition, approximately 308 million people globally were diagnosed as impaired glucose tolerance (IGT) (International Diabetes Federation, 2009) in 2007, indicating a rising projection for diabetes number in the future. High pandemic of diabetes and its macro-implications cause billions dollars in losses, increment in household burden, and low productivity in the global economics (Zhang et al., 2010). Thus, the research on diabetes is crucial because of its fast growing number, high mortality rate, serious implications and global economic losses especially in developed and developing countries (Engelgau et al., 2004).

Numerous medications have been introduced since the last few decades to manage the hyperglycemic conditions, and most of it is focusing on insulin secretory and action, and its target organ and tissues. The prescription of synthetic medicines such as thiazolidinediones are clinically shown to improve the diabetic condition by increasing the insulin sensitivity, reducing the blood sugar level, and improving the lipid profile, but it increases the incidence of weight gain (Kelly et al., 1999), increased risk of cardiovascular disease (Lipscombe, 2008), edema and anemia (Inzucchi, 2002) also have been reported. Metformin (biguanide), a commonly used diabetic drugs has high anti-diabetic efficacy compared to α -glucosidase inhibitors (AGIs), and safer than sulfonylurea (SU) (Johansen, 1999), yet, it is also associated with gastrointestinal distress (Bailey and Turner, 1996). Some diabetic medications such as phenformin (biguanide) and troglitazone (thiazolidinediones) were also banned after being released for a few years in the market because of lactic acidosis (Kolata, 1979) and idiosyncratic hepatocellular injuries (Murphy et al., 2000) respectively. Hence, no promises can be compromised on the safety of taking these synthetic medications over a long period of time because some drugs will only show adverse effects after long period of consumption. The consumption of synthetic drugs will show impressive result on diabetic condition, but at the same time it slowly creates other health problems. Thus, an invention of new products should be continuously created to treat diabetes naturally without or with reduced harming effects.

Since ancient time, the consumption of fruits, vegetables and also herbs for the treatment of diabetes have been introduced by traditional practitioners to several populations of diabetes patients and the tradition is still in practice now. In India, *Buteamonosperma* (Somani et al., 2006) and *Scopariadulcis* (Latha et al., 2004) have been conventionally used as anti-diabetic prescription in several regions. *Nigella sativa* and *Olea europaea* are plants used by oldfolks in certain regions of Morocco in the management of diabetes mellitus (Tahraoui et al., 2007). Nowadays, many food products from plant sources have been produced and introduced as an alternative or complementary to diabetic medication. Complementary and alternative medicine (CAM) has also been used in several regions and countries such as United States, Nigeria, Africa, Asia and South America (Egede et al., 2002; Gbolade, 2009). The products are getting more attention because of its natural properties which are safer and more cost effective than synthetic drugs.

Canarium odontophyllum Miq. is one of the most popular indigenous and underutilised fruits in Sarawak. It is called *dabai* by the locals and getting much attention during the peak season. *Dabai* is not only delicious, but it also provides high energy and contains protein, vitamins, minerals and also polyphenolic compound (Voon and Kueh, 1999; Chew et al., 2011). The beauty of its purple colour also indicates that this fruit contains high level of antioxidant compounds such as anthocyanin and anthocyanidin (Chew et al., 2012). Utsunomiya et al. (2005) has shown the positive impact of purple-coloured plum fruits against diabetes by its anti-hyperglycemia and insulin sensitizer properties. Natural antioxidant compounds from plant sources are found to be beneficial as anti-diabetic agents. Even though several studies have showed positive contribution of the *dabai* fruits to cardiovascular diseases, as yet there has been no study conducted to determine the contribution of the plant on the management of diabetes conditions.

1.3 Significance of the Study

Dietary constituents and natural products have been recognised as one of the major interest in numerous studies towards a better and healthier lifestyle. Nowadays, considerable attention is focussing on the usage of those components as alternative or complimentary treatments for many diseases such as cardiovascular diseases, Alzheimer, cancers and also diabetes. Studies on natural products are important to find a safer product with the same effectiveness and cheaper than synthetic drugs.

Plants polyphenol compounds are associated in the prevention and treatment of degenerative and non-communicable diseases because of its role as natural antioxidants that fight against free radicals. *Dabai* not only contains high energy, but it also exhibit high antioxidant properties and contain numerous phenolic acids and flavonoids. Moreover, *dabai* also showed a positive relation against cardiovascular disease developed in animal model by its anti-hypercholesterolaemic properties and plaque reduction (Shakirin et al., 2012). Thus, this fruit has a potential to be used as natural anti-

diabetic prescription either as a complement to the synthetic ones or as a direct alternative. Other than that, investigation on the effects of this fruits extract on diabetes parameters will also contribute useful knowledge to be used for further research. Moreover, this study also contributes additional knowledge on the utilization of underutilised fruit grown in Sarawak.

Not only the nutritious properties of *dabai* will give benefits to the health, its tasty and addictive effect also has a positive impact against the economic aspects. *Dabai* has been domesticated and cultivated extensively in Sarawak as it has an immediate potential for commercial exploitation. It can contribute significantly to agro-biodiversity, food security, nutrition and household income. Thus, this study could also contribute to the commercialization of *dabai* in exploitation of the cultivation.

1.4 Objectives

1.4.1 General Objective

To study the effect of *dabai* (*Canarium odontophyllum*) fruit extract on biochemical parameters of obese-diabetic rats.

1.4.1 Specific objectives

1. To determine the antioxidant activity (DPPH, BCB and ORAC assay) and polyphenol profile of *dabai* extract by using HPLC.
2. To determine the effect of *dabai* extract on body weight, BMI, food and water intake of obese-diabetic rats.
3. To evaluate the effect of *dabai* extract on plasma glucose level, oral glucose tolerance test (OGTT), lipid profile (total cholesterol, triglyceride, HDL-c and LDL-c) and insulin profile (insulin level, sensitivity and resistance) on obese-diabetic rats.
4. To determine the effect of *dabai* extract on endogenous total antioxidant status (TAS) and antioxidant enzymes, glutathione peroxidase (GPx) and superoxide dismutase (SOD) activities in obese-diabetic rats.

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