



**UNIVERSITI PUTRA MALAYSIA**

***EFFECTS OF *Ficus deltoidea* JACK AND VITEXIN ON PANCREAS,  
BRAIN, KIDNEY AND BONE OF STREPTOZOTOCIN-INDUCED  
DIABETIC RATS***

**NURDIANA BINTI SAMSULRIZAL**

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DIABETIC RATS**

By

**NURDIANA BINTI SAMSULRIZAL**

**Thesis Submitted to the School of Graduate Studies, Universiti Putra  
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Philosophy**

**November 2017**

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

**EFFECTS OF *Ficus deltoidea* JACK AND VITEXIN ON PANCREAS, BRAIN, KIDNEY AND BONE OF STREPTOZOTOCIN-INDUCED DIABETIC RATS**

By

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**November 2017**

**Chairman : Goh Yong Meng, PhD**

**Faculty : Veterinary Medicine**

Hyperglycaemia is the predominant cause of tissue damage and other systemic complications through oxidative stress. In diabetic patients, hyperglycaemia is associated with dearrangement of glycemic control. Limiting oxidative stress injuries using antioxidants therefore would be a logical approach to reduce hyperglycaemia and prevent further diabetes complications. *Ficus deltoidea* is a plant high in antioxidant compound content such as vitexin. Improvements in fasting blood glucose and antioxidant activities have indeed been reported following treatment with *F. deltoidea* and vitexin. However, the potential of *F. deltoidea* and vitexin in delaying diabetes-related complications remains to be examined. In this regard, the study aimed to examine the effects of *F. deltoidea* and vitexin on the pancreas, brain, kidney and bone of streptozotocin (STZ)-treated rats. Intraperitoneal injection of STZ (60 mg/kg) was used to induce hyperglycaemia in rats. Methanol extract of *F. deltoidea* and vitexin was then given by oral-gavage for eight weeks. The effects of *F. deltoidea* and vitexin on the pancreas, brain, kidney and bone were further evaluated in four interlinked experiments. The novelty of this study is that Fourier transform infrared (FT-IR) spectroscopy has been introduced as a diagnostic approach to examine metabolic fingerprinting related to the tissue changes showing by biochemical and histological analysis, Morris Water Maze (MWM) test, micro-computed tomography (micro-CT) and fatty acid profiles. The present study demonstrates, for the first time, that *F. deltoidea* treatment was able to preserve pancreatic islet structure, improve learning and memory ability, mitigate renal injury and prevent bone loss in STZ-treated rats. It was also found that *F. deltoidea* resulted in a significant reduction in circulating amylin and an increase in serum insulin and osteocalcin levels. Additionally, the results showed that *F. deltoidea* treatment was associated with increased pancreatic, brain and

kidney antioxidant activity. Although structural and functional improvement of the pancreas and brain was seen, vitexin treatment is associated with an increased risk of acute kidney injury and osteopenia. This might be explained by an increased serum fructose. In conclusion, *F. deltoidea* increased insulin secretion, in part, by reversing STZ-induced organ damage in the pancreas, brain, kidney and bone of rats. This could be related to the optimization of oxidant-antioxidant balance in the tissue.



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

**KESAN *Ficus deltoidea* JACK DAN VITEXIN PADA PANKREAS, OTAK,  
BUAH PINGGANG DAN TULANG TIKUS DIABETIK ARUHAN  
STREPTOZOTOCIN**

Oleh

**NURDIANA BINTI SAMSULRIZAL**

**November 2017**

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Umum mengetahui bahawa hiperglikemia merupakan faktor utama kerosakan tisu dan komplikasi sistemik melalui pengaktifan tekanan oksidatif. Hiperglikemia pada pesakit diabetes lazimnya dikaitkan dengan gangguan metabolisme glukosa. Oleh itu, meminimakan kerosakan tisu melalui rawatan antioksidan berkemungkinan mampu mengurangkan hiperglikemia dan mencegah komplikasi diabetes lanjut. *F. deltoidea* adalah tumbuhan yang kaya kandungan bahan antioksidan seperti vitexin. Kajian terdahulu menunjukkan penggunaan *F. deltoidea* dan vitexin telah berjaya mengurangkan kandungan glukosa darah dan meningkatkan aktiviti antioksidan pada model haiwan. Walau bagaimanapun, potensi rawatan *F. deltoidea* dan vitexin untuk mencegah komplikasi yang berkaitan dengan diabetes masih perlu dikaji. Sehubungan itu, kajian ini bertujuan untuk menilai kesan penggunaan *F. deltoidea* dan vitexin pada tisu pankreas, otak, buah pinggang and tulang tikus diabetik aruhan streptozotocin (STZ). Model tikus diaruh menggunakan suntikan intraperitoneal STZ pada dos 60 mg/kg. Rawatan *F. deltoidea* dan vitexin kemudiannya diberikan selama lapan minggu berturut-turut melalui kaedah suap paksa. Kesan rawatan *F. deltoidea* dan vitexin pada tisu pankreas, otak, buah pinggang dan tulang dinilai melalui empat eksperimen berangkai. Unikunya, spektroskopi Fourier transform infrared (FT-IR) digunakapakai sebagai pendekatan baru untuk mengesan pengenalan metabolik bersangkutan dengan perubahan yang diperoleh dari analisa biokimia dan histologi, Morris water maze (MWM), tomografi mikrokomputer (mikro-CT) dan profil asid lemak. Hasil kajian menunjukkan bahawa rawatan *F. deltoidea* boleh memelihara struktur pankreas, meningkatkan keupayaan pembelajaran dan ingatan, mengurangkan kecederaan buah pinggang dan mencegah hakisan tulang dalam tikus-tikus aruhan STZ. Rawatan ini juga didapati berupaya mengurangkan aras amylin serta

meningkatkan kepekatan insulin dan osteocalcin dalam serum. Selain itu, rawatan *F. deltoidea* didapati mampu meningkatkan aktiviti antioksidan pada tisu pankreas, otak dan buah pinggang. Walaupun terdapat perubahan positif pada struktur serta fungsi pankreas dan otak, rawatan vitexin berisiko meningkatkan kegagalan buah pinggang dan osteopenia. Ini berkait rapat dengan kandungan fruktosa yang tinggi dalam serum. Secara konklusinya, peningkatan rembesan insulin dalam tikus yang terawat-*F. deltoidea* dipengaruhi oleh pemulihan tisu pankreas, otak, buah pinggang dan tulang. Perubahan ini mempunyai kaitan dengan pengoptimalan keseimbangan oksidan-antioksidan dalam tisu.



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I certify that a Thesis Examination Committee has met on 21 November 2017 to conduct the final examination of Nurdiana binti Samsulrizal on her thesis entitled "Effects of *Ficus deltoidea* Jack and Vitexin on Pancreas, Brain, Kidney and Bone of Streptozotocin-Induced Diabetic Rats" 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

AGEs	advanced glycation end products
ANOVA	analysis of variance
AR	aldose reductase
ATP	adenosine triphosphate
AUC	area under curve
A $\beta$	$\beta$ -amyloid
BALP	bone-specific alkaline phosphatase
BF <sub>3</sub>	boron trifluoride
BMD	bone mineral density
BV/TV	bone volume ratio
Ca	calcium
cAMP	cyclic adenosine monophosphate
Cl	chloride
°C	degree Celsius
°C/min	degree Celsius per minute
DHA	docosahexaenoic acid
DNA	deoxyribonucleic acid
DPD	deoxypyridinoline
EDTA	ethylenediaminetetraacetic acid
ELISA	enzyme-linked immunosorbent assay
FAME	fatty acid methyl esters
FT-IR	Fourier transform infrared
GAPDH	glyceraldehyde-3-phosphate dehydrogenase
GC	gas chromatography
GFAT	glutamine: fructose-6-phosphate aminotransferase
GFR	Glomerular filtration rate
GK	glucokinase
GLUT2	glucose transporters 2
GPx	glutathione peroxidase
GR	glutathione reductase
H&E	hematoxylin and eosin
H <sub>2</sub> O <sub>2</sub>	hydrogen peroxide
HBP	hexosamine biosynthetic pathway
HCA	hierarchical cluster analysis
HOMA	homeostatic model assessment
HPLCMS	High-performance liquid chromatography-mass spectrometry
HRP	horseradish peroxidase
HU	Hounsfield units

ICV	intracerebroventricular
IPGTT	intraperitoneal glucose tolerance test
IPITT	intraperitoneal insulin tolerance test
K	potassium
K <sub>2</sub> HPO <sub>4</sub>	dipotassium hydrogen phosphate trihydrate
KCl	potassium chloride
KOH	potassium hydroxide
MDA	malondialdehyde
micro-CT	micro-computed tomography
mid-IR	mid-infrared
mmol/L	millimoles per litre
MUFA	monounsaturated fatty acid
MWM	Morris Water Maze test
Na	sodium
NADH	nicotinamide adenine dinucleotide
NADPH	nicotinamide adenine dinucleotide phosphate
ng/mL	nanogram per milliliter
nmol/mg	nanomoles per milligrams
<i>Ocn</i> <sup>-/-</sup>	osteocalcin knockout
P	phosphorus
PKC	protein kinase C
PPAR <sub>γ</sub>	peroxisome proliferator-activated receptor gamma
PUFA	polyunsaturated fatty acids
QTOF-LCMS	Quadrupole time of flight liquid chromatography mass spectrometry
QUICKI	quantitative insulin sensitivity check index
ROI	region of interest
ROS	reactive oxygen species
SD	standard deviation
SDH	sorbitol dehydrogenase
SFA	saturated fatty acid
SOD	superoxide dismutase
STZ	Streptozotocin
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
TBARS	thiobarbituric acid reactive substances
TbN	trabecular number
TbSp	trabecular separation
TMB	trimethoxybenzoate
Tris-HCl	tris hydrochloride
U/mg	units per milligrams



# CHAPTER 1

## GENERAL INTRODUCTION

### 1.1 Context and motivation

Diabetes mellitus is characterized by hyperglycaemia due to the inability of the body to autonomously regulate the blood glucose levels (Brereton *et al.*, 2014). It currently affects about 422 million people worldwide (World Health Organization, 2016), out of which 3.3 million of them have been diagnosed in Malaysia (Hussein *et al.*, 2015). Notable in the latter report, diabetes causes 1.5 million deaths in 2012 which derives primarily from complications of persistent hyperglycaemia (Krug, 2016). Pinhas-Hamiel and Zeitler (2005) pointed out that diabetes becomes more common in young adults, adolescents and occasionally, in children. In fact, hyperglycaemia is even postulated as contributing factor for cancer progression (Ryu *et al.*, 2014; Lee *et al.*, 2016). Despite optimal treatment regimens with insulin or oral diabetes medications, glucose fluctuation in a person with diabetes remains a major challenge (Aronoff *et al.*, 2004). These observations suggest that diabetes complications can be overcome, at least, by restoring glucose homeostasis. Therefore, the effective therapeutic strategy in restoring glucose homeostasis requires further investigation.

It is worth noting that acute glucose fluctuations are responsible to influence the magnitude of oxidative stress (Monnier *et al.*, 2006; Wu *et al.*, 2016). Hyperglycaemia-induced oxidative stress has been postulated as a possible mechanism for diabetes-associated tissue and other systemic complications (Giacco and Brownlee, 2010; Asmat *et al.*, 2016). Indeed, a myriad of diabetic tissue damage reported in animal and human studies are driven by oxidative stress regardless of the type of diabetes (Saito *et al.*, 2014; Li *et al.*, 2015). What is more, these changes are sustained even after hyperglycaemia control is therapeutically achieved (Intine and Sarras, 2012). This is supported by the fact that majority of diabetes treatment expenditures were spent treating diabetes-related complications (Barquera *et al.*, 2013). Novel approaches for reversing hyperglycaemic memory and tissue damage, in particular glucose regulation complex are therefore urgently needed.

### 1.2 Statement of the problem

Over the last few years, glucose regulation has been referred to as a multiorgan process (DeFronzo *et al.*, 2012). There are evidences that show the pancreas, brain, kidney and bone play critical roles in orchestrating the control of glucose (Marty *et al.*, 2007; Gerich, 2010; Faienza *et al.*, 2015). The relationship between blood glucose control, multiplicity of hormonal and



neuronal signals by these organs has also been reported in numerous studies (Wei *et al.*, 2014; Clemens and Karsenty, 2011). From another perspective, it is well established that dysregulation of glucose homeostasis aggravate oxidative damage by augmenting reactive oxygen species (ROS) production. Pathological changes in the pancreas, brain, kidney and bone are indeed more common in those with diabetes. Despite these observations, the potential link between tissue regeneration and glucose-lowering action is rarely discussed.

Replenishing endogenous insulin, buffering the generation of ROS and optimizing the oxidant-antioxidant balance has recently been identified as the most promising strategies for ameliorating diabetes-induced tissue damage (Kashihara *et al.*, 2010; Pimson *et al.*, 2014). Although exogenous insulin and oral diabetes medications offer regenerative effect on certain tissue (Marycz *et al.*, 2016), the risks appear to outweigh the development of metabolic syndrome and complications. This is mainly due to the difficulties in managing blood glucose fluctuations. In fact, insulin treatment also seems ineffective in the restoration of biomechanical deterioration of bone (Erdal *et al.*, 2012).

The past decade has witnessed an increasing interest in exploring medicines derived from plants. Both experimental and clinical studies suggest that the plant based drug is inherently safer and less toxic than pharmaceuticals (Katiyar *et al.*, 2012). In fact, multiple evidence strands suggest that the plant extract exerts tissue protective effects (Ezejiolor *et al.*, 2013; Wang and Huang, 2014). *F. deltoidea* has been reported to have a glucose-lowering effect and exhibit antioxidant activity (Adam *et al.*, 2010; Bhardwaj *et al.*, 2015). Similar findings were also noticed in other study related to vitexin, the compound marker of *F. deltoidea* (Choo *et al.*, 2012). However, less firm evidence comes from data to explain the role of *F. deltoidea* and vitexin in delaying progression of diabetic tissue damage, particularly on pancreas, brain, kidney and bone.

### **1.3 Objectives of the Study**

The work presented in this thesis investigates the changes in the pancreas, brain, kidney and bone as an integrated functional unit following *F. deltoidea* and vitexin treatment with the purpose of describing the relationships between reversing tissue injury and glucose-lowering action. It was hypothesized that tissue regeneration could be the transmissible element in the lowering of blood glucose and these changes can be determined from the FT-IR spectral. On the basis of these hypotheses, the present study was designed according to the following objectives:

1. To characterize histological and oxidative stress changes in the pancreas of STZ-induced diabetic rats following *F. deltoidea* and vitexin treatment.
2. To identify the effects of *F. deltoidea* and vitexin treatments on behavioural, gyrification patterns and brain oxidative stress markers in diabetic rats.
3. To investigate renal structural and functional changes occurring in STZ-treated rats after *F. deltoidea* and vitexin supplementation.
4. To determine the effects of *F. deltoidea* and vitexin on bone histomorphometry, biochemical and oxidative stress markers in diabetic rats.

#### **1.4 Significance of the Study**

The thesis strives to provide valuable information that maintenance of normal glucose homeostasis requires a complex, highly integrated interaction among the pancreas, brain, kidney, and bones. In this regard, an overview of tissue damages related to hyperglycaemia has been shown to demonstrate the associations between inter-organ functions and glucose-lowering action. Methodologically, the thesis introduces a novelty detection approach adopted by FT-IR spectroscopy for examining metabolic fingerprinting related to tissue changes. The study also provides evidence that the brain can be distinguished from the cranium without contrast enhancement using micro-CT. The availability of a rapid and reagent-free method in detecting biochemical and histological changes associated with diabetes may greatly speed up and simplify the diagnosis process. This could also be useful in the future to improve antidiabetic treatment and develop new selective therapies. Above all, this study justifies the use of *F. deltoidea* leaves extract and vitexin as an alternative therapy in the management of diabetes-associated tissue damage.

#### **1.5 Structure and outline of the thesis**

This thesis is arranged into nine different chapters. Chapter 2 briefly describes the role of pancreas, brain, kidney and bone in glucose homeostasis. The latter part of literature review focussed on the pathogenic mechanisms of hyperglycaemia-induced tissue damages. Aspects that are relevant to the project are reviewed in order to provide justification for the work carried out and insights into a new possibility in diabetes care by reprogramming cells to repair damaged tissue. Further, this chapter highlights the advantages of herbal medicine particularly on *F. deltoidea* as desirable therapeutic option for enhancing tissue repair. Current approaches of tissue damage detection are summarized at the end of Chapter 2. Description of the general approach and methodology for this study is given in Chapter 3.

In the framework of hyperglycaemia related to tissue damage, the following chapters were included to explore the pathological changes in STZ-treated rats. Chapter 4 serves to illustrate changes in the pancreas histology, antioxidant enzymes, insulin secretion and serum amylin related to fasting blood glucose. The beneficial effect of *F. deltoidea* and vitexin as a therapeutic agent for the management of diabetes-related brain damage was further investigated in Chapter 5. Chapter 6 designed to explore the effects of *F. deltoidea* and vitexin on renal changes, while Chapter 7 elaborates the effect *F. deltoidea* and vitexin on bone loss occurring in STZ-treated rats.

All changes described in Chapter 4, 5, 6 and 7 were summarized and discussed in Chapter 8. This chapter is meant to emphasize the relationship between inter-organ functions and antidiabetic activity. Finally, Chapter 9 concludes the thesis with some closing remarks. Additionally, the outline of possible further research directions is provided.

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