UNIVERSITI PUTRA MALAYSIA

EVALUATION OF IN VITRO ANTIDIABETIC MECHANISMS OF METHANOLIC EXTRACTS FROM FOUR Ficus deltoidea Jack VARIETIES

NURSHIEREN YAHAYA

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By

NURSHIEREN YAHAYA

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

March 2020

I dedicate this thesis for my families, future generations

and the enthusiasts of Malaysia's herbal medicines

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

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March 2020

Chairman: Muhajir Hamid, PhD
Faculty: Biotechnology and Biomolecular Sciences

Diabetes Mellitus has been a global metabolic disorder and affected people of various ages. In this research, four varieties of methanolic *Ficus deltoidea* extracts containing natural products that possess anti-diabetic properties has been studied. The study was carried out because antidiabetic synthetic drugs have been reported to have negative side effects on diabetes patients. Therefore, the study was done to elucidate insulin-secreting activity towards the beta pancreatic cell, to elucidate glucose uptake activity in insulin targeted cells, to determine the potential of insulin-sensitizing activity in adipocytes cells and to determine the potential of antiglycation activities of four methanolic *Ficus deltoidea* varieties. The viability study which manifests viability assay has shown that methanolic *Ficus deltoidea* variety *deltoidea*, *angustifolia* and *motleyana* does not toxic towards the treated cells with the highest viability were portrayed by the highest viability can be seen when treated with 500 µg/ml of methanolic extract *Ficus deltoidea* variety *angustifolia* with 151.42 ± 0.08 percent ($p<0.001$) on beta pancreatic cell, 1000 µg/ml of methanolic extract *Ficus deltoidea* variety *angustifolia* with 122.66 ± 1.92 percent ($p<0.01$) on L6 muscle cell and the highest viability can be seen at 100 µg/ml when treated with methanolic *Ficus deltoidea* variety *motleyana* at 110.58 ± 3.45 percent on 3T3F442A adipocytes cell but not significant. Besides, insulin secretion study conducted with insulin secretion assay showed methanolic extracts of *Ficus deltoidea* varieties can stimulate insulin release from pancreatic cells through the K_{ATP} independent pathway. The highest insulin secretion was shown by methanolic extract *Ficus deltoidea* variety *deltoidea* with 6.24 fold ($p<0.001$). In addition, the extracts able to stimulate glucose uptake in basal and insulin-mediated state where the highest uptake can be seen in insulin-mediated state of L6 muscle cell treated with methanolic extract *Ficus deltoidea* variety *motleyana* with 3.65 fold ($p<0.001$) when compared to control and 2.90 fold ($p<0.001$) when compared to insulin 100 nM. Apart from that the highest uptake can be seen in insulin-mediated state of 3T3F442A adipocyte cell treated with methanolic extract *Ficus deltoidea* variety *motleyana* with 1.39 fold ($p<0.001$) when compared to control and 1.27 fold ($p<0.001$) when compared to insulin 100 nM. All of the extracts follow the phosphatidylinositol-3-kinase-independent

pathway except for *Ficus deltoidea* variety *motleyana* where when treated to 3T3F442A cell, the extract does not follow both of phosphatidylinositol-3-kinase-dependent and independent pathway. While in gene expression study through using Quantigene assay kit, showed methanolic *Ficus deltoidea* variety *bilobata* as the highest expression for phosphatidylinositol-3-kinase-dependent pathway with 1.24 fold in 6 hours while *Ficus deltoidea* variety *motleyana* showed the highest expression for phosphatidylinositol-3-kinase-independent pathway with 1.21 fold in 6 hours. All four varieties at a concentration of 100 μM in insulin-mediated state shown a significant glucose uptake activity in insulin resistance cell with the best secretion of leptin and inhibition of tumor necrosis factor-α was significantly recorded by methanolic extract *Ficus deltoidea* variety *angustifolia* with 2.56 fold ($p<0.001$) and 0.73 fold ($p<0.001$). Last but not least, the highest antiglycation activity was exhibited by methanolic *Ficus deltoidea* variety *bilobata* with 78.92 percent of advanced glycation endproducts inhibition formation along with the highest detection of fructosamine inhibition with 86.40 percent reduction. While *Ficus deltoidea* variety *deltoidea* showed significant results with protein thiol preservation of 6.14 fold ($p<0.001$) and protein carbonyl reduction with 1.76 fold ($p<0.001$). Total phenolic content assay showed that methanolic *Ficus deltoidea* variety *bilobata* to have highest phenolic content of 299.78 ± 2.88 mg GAE/ g of extract ($p<0.001$). The varieties also showed significant antioxidant activities. In conclusion, methanolic *Ficus deltoidea* extract showed that most extract follow independently of ATP-sensitive potassium channel in insulin secretion activity. Apart from that, the extracts follow glucose uptake phosphatidylinositol-3-kinase independent pathway, able to sensitize insulin and inhibit advanced glycation formation. Therefore, it is suggested that methanolic *Ficus deltoidea* extracts can be a promising candidate to be used as phytopharmaceutical agents to manage diabetes mellitus.

Keywords : Antidiabetic, *Ficus deltoidea*, insulin, glucose uptake, antiglycation

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KAJIAN *IN VITRO* MEKANISMA ANTIDIABETIK OLEH EMPAT JENIS METANOLIK EKSTRAK VARIATI *Ficus deltoidea* Jack

Oleh

NURSHIEREN YAHAYA

Mac 2020

Pengerusi: Muhajir Hamid, PhD
Fakulti: Bioteknologi dan Sains Biomolekul

Kencing manis telah menjadi gangguan metabolisme global dan boleh didapati dalam pelbagai peringkat umur. Dalam kajian ini, empat jenis ekstrak standard metanolik *Ficus deltoidea* mengandungi produk semula jadi yang mempunyai sifat anti-kencing manis. Kajian telah dijalankan kerana ubat sintetik antidiabetes telah dilaporkan mempunyai kesan sampingan yang negatif kepada pesakit kencing manis. Oleh itu, kajian ini telah dilakukan untuk menjelaskan aktiviti insulin ke arah sel pankreas beta, mendapatkan semula aktiviti pengambilan glukosa dalam sel sasaran insulin, mengkaji potensi aktiviti insulin-sensitif dalam sel adiposit dan mengkaji potensi aktiviti antiglikasi empat jenis ekstrak standard metanolik *Ficus deltoidea*. Kajian daya maju telah menunjukkan bahawa ekstrak standard metanolik *Ficus deltoidea* jenis *deltoidea*, *angustifolia* dan *motleyana* tidak toksik terhadap sel yang dirawati. Daya maju yang paling tinggi direkodkan ialah 500 µg/ml ekstrak metanolik *Ficus deltoidea* variati *angustifolia* dengan peratusan 151.42 ± 0.08 persen ($p<0.001$) ke atas sel pankreatik beta, 1000 µg/ml ekstrak metanolik *Ficus deltoidea* variati *angustifolia* dengan peratusan 122.66 ± 1.92 persen ($p<0.01$) ke atas sel otot L6 dan 100 µg/ml ekstrak metanolik *Ficus deltoidea* variati *motleyana* dengan peratusan 110.58 ± 3.45 persen ke atas 3T3F442A sel adiposit tetapi tidak menunjukkan kesan signifikan. Selain itu, kajian rembesan insulin menggunakan metod kajian perembesan insulin menunjukkan ekstrak metanolik *Ficus deltoidea* boleh merangsang pembebasan insulin dari sel pankreas melalui laluan bergantung K_{ATP}. Penghasilan insulin yang paling tinggi ditunjukkan oleh ekstrak metanolik *Ficus deltoidea* variati *deltoidea* dengan 6.24 kali ganda ($p<0.001$). Selain itu, ekstrak metanolik daripada semua variati *Ficus deltoidea* mampu meningkatkan pengambilan glukosa di peringkat basal dan pengantaraan insulin di mana pengambilan glukosa yang paling tinggi adalah dalam keadaan pengantaraan glukosa di dalam sel otot L6 oleh metanolik ekstrak *Ficus deltoidea* variati *motleyana* dengan 3.65 kali ganda ($p<0.001$) apabila dibandingkan dengan kumpulan kawalan dan 2.90 kali ganda ($p<0.001$) apabila dibandingkan dengan insulin 100 nM. Selain daripada itu, pengambilan glukosa tertinggi di dalam sel 3T3F442A adiposit ditunjukkan oleh ekstrak metanolik *Ficus deltoidea* variati *motleyana* dengan 1.36

kali ganda ($p<0.001$) dibandingkan dengan kumpulan kawalan dan 1.27 kali ganda ($p<0.001$) apabila dibandingkan dengan insulin 100 nM. Semua ekstrak mampu merangsang pengambilan glukosa di dalam keadaan basal dan pengantaraan insulin dan mengikuti laluan bebas phosphatidylinositol-3-kinase kecuali untuk *Ficus deltoidea* variati *motleyana* di mana apabila diuji sel 3T3F442A, ekstrak tidak mengikuti kedua-dua laluan bebas phosphatidylinositol-3-kinase. Dalam kajian ekspresi gen, ekstrak standard metanolik *Ficus deltoidea* variati *bilobata* menunjukkan keputusan tertinggi untuk laluan phosphatidylinositol-3-kinase dengan keputusan 1.24 kali ganda dalam masa 6 jam manakala *Ficus deltoidea* jenis *motleyana* menunjukkan keputusan tertinggi bagi laluan bebas phosphatidylinositol-3-kinase dengan keputusan 1.21 kali ganda dalam masa 6 jam. Kesemua empat jenis pada kepekatan 100 μM dalam keadaan bersama insulin telah menunjukkan aktiviti pengambilan glukosa yang signifikan dalam sel rintangan insulin dengan rembesan leptin dan perencatan faktor tumor nekrosis-α telah direkodkan dengan ketara dan terbaik oleh ekstrak metanolik *Ficus deltoidea* variati *angustifolia* dengan 2.56 kali ganda ($p<0.001$) serta 0.73 kali ganda ($p<0.001$). Akhir sekali, aktiviti antiglikasi tertinggi telah dipamerkan oleh standard metanolik *Ficus deltoidea* jenis *bilobata* dengan 78.92 persen penghalangan kepada pembentukan produk glikasi lanjutan manakala pengesanan tertinggi perencatan fruktosamin menunjukkan 86.40 persen penurunan. Manakala *Ficus deltoidea* jenis *deltoidea* menunjukkan keputusan yang signifikan dengan pengesanan protein thiol bersama keputusan 6.14 kali ganda ($p<0.001$) dan peratusan penghalangan pembentukan protin karbonil iaitu sebanyak 1.76 kali ganda ($p<0.001$). Ujian Jumlah Kandungan Fenolik pula mencatatkan ekstrak metanolik *Ficus deltoidea* variati *bilobata* mempunyai kandungan fenolik tertinggi iaitu 299.78 ± 2.88 mg GAE/ g ekstrak ($p<0.001$). Semua ekstrak juga menunjukkan signifikasi di dalam aktiviti antioksidan. Sebagai kesimpulan, kebanyakan ekstrak metanolik daripada variati *Ficus deltoidea* menunjukkan laluan bebas daripada saluran potasium ATP-sensitif di dalam aktiviti perembesan insulin. Selain itu, aktiviti pengambilan glukosa menunjukkan kebanyakan ekstrak metanolik *Ficus deltoidea* mengikuti laluan bebas fosfatidilinositol-3-fosfat. Ekstrak tersebut juga dapat menjadikan sel lebih sensitif terhadap insulin dan mampu mengalang pembentukan produk glikasi lanjutan. Oleh itu, adalah dicadangkan bahawa ekstrak metanolik *Ficus deltoidea* boleh menjadi calon yang menjanjikan kesan positif sebagai agen fitofarmaseutikal bagi membendung penyakit kencing manis.

Kata kunci : Antidiabetik, *Ficus deltoidea*, insulin, pengambilan glukosa, antiglikasi

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Muhajir Hamid, PhD
Associate Professor
Faculty of Biotechnology and Biomolecular Sciences
Universiti Putra Malaysia
(Chairman)

Norazizah Shafee, PhD
Professor
Faculty of Biotechnology and Biomolecular Sciences
Universiti Putra Malaysia
(Member)

Zainah Adam, PhD
Research Officer
Medical Technology Department
Malaysian Nuclear Agency
(Member)

_____
ZALILAH MOHD SHARIFF, PhD
Professor and Dean
School of Graduate Studies
Universiti Putra Malaysia

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AMPK	Adenosine 5′ Monophosphate-activated Protein Kinase
AGEs	Advanced Glycation Endproducts
AKT	Protein Kinase B
ALLN	N-acetyl-Leu-Leu-Norleu-al
ANOVA	Analysis of Variance
ATP	Adenosine Triphosphate
cAMP	Cyclic Adenosine Monophosphate
CAP	Catabolite Activator Protein
cfDNA	Cell-free Deoxyribonucleic Acid
DAG	Diacylglycerol
DMEM	Dulbecco's Modified Eagle Medium
DNA	Deoxyribonucleic Acid
DPP-4	Dipeptidyl Peptidase-4
DPPH	2,2-diphenyl-1-picrylhydrazyl
ELISA	Enzyme-Linked Immunosorbent Assay
GDM	Gestational Diabetes Mellitus
GDP	Guanosine diphosphate
GLP-1	Glucagon-like Peptide 1
GTP	Guanosine Triphosphate
IDF	International Diabetes Federation
IFN- γ	Interferon-gamma
IL-6	Interleukin 6
IP3	Inositol Triphosphate
IRS-1	Insulin receptor Substrate 1
JNK	c-Jun N-terminal Kinase

KATP	ATP-sensitive potassium
KRB	Kreb's Ringer Buffer
MAPK	Mitogen-Activated Protein Kinase
mRNA	Messenger Ribonucleic Acid
mTOR	Mechanistic Target of Rapamycin
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
NF-kB	Nuclear Factor kappa B
PBS	Phosphate Buffer Saline
PI3K	Phosphatidylinositol 3-kinase
PPAR	Peroxisome proliferator-activated receptor
RAGE	Receptor Advanced Glycation Endproducts
ROS	Reactive Oxygen Species
RPMI 1640	Roswell Park Memorial Institute 1640
SDS	Sodium Dodecyl Sulfate
SGLT-2	Sodium-glucose co-transporter-2
SNP	Single Nucleotide Polymorphism
STAT3	Signal Transducer and Activator of Transcription 3
TLR-4	Toll-Like Receptor 4
TNF-α	Tumor Necrosis Factor Alpha

CHAPTER 1

INTRODUCTION

1.1 Background of Study

Diabetes has occurred worldwide. This metabolic disease has affected all age stages and occurs etiologically in several types. The first type of diabetes mellitus occurs when the beta cell is impaired and ultimately results in the need for insulin injection. The second type of diabetes mellitus is due to insulin resistance, where the insulin-targeting cell does not respond to insulin and is therefore unable to regulate blood glucose levels. Part of that other form of diabetes is the hybrid type in which type 1 diabetes has been detected in adult life preceding type 2 diabetes mellitus. Another form of diabetes is gestational diabetes, which developed during pregnancy due to placental activity. The new estimate in adults with diabetes mellitus showed that large burdens were recorded, particularly in developing countries, where almost 382 million people were affected by metabolic disorder in 2013, and 592 million people were expected to have this disease by 2035 (Guariguata *et. al*., 2014). In addition, IDF diabetes atlas has shown that the prevalence of this disease is estimated to be 451 million diabetics in 2017 and an additional 242 million in 28 years (Cho *et. al*., 2018). Metabolic disorder is the top ten cause of death worldwide in the 2013 Global Burden of Disease Study (Naghavi *et. al*., 2015) while the 2013 Malaysian study reported that diabetes has become one of the leading causes of death in women (Omar *et. al*., 2019).

Diabetes mellitus has had a negative impact on several aspects. The most common impact is the cost burden where higher costs are needed for catering patients with diabetes mellitus complications in health care (Domeikiene *et. al*., 2014). It has been estimated that by 2030 the cost of the economic burden of diabetes is more than USD 2.1 trillion compared to 2015, where the cost of the burden is USD 1.3 trillion (Bommer *et. al*., 2018). IDF diabetes atlas also reported that the average cost per person worldwide in 2014 ranged from USD 1.583 to USD 2.842, while North America and the Caribbean region had the highest annual expenditure per person, while South East Asia had the lowest annual cost per person for diabetes (Da Rocha Fernandes *et. al*., 2016). Apart from that, looking at the national economic burden in Iran, patients with type 2 diabetes need higher costs compared to other health care costs, while in Malaysia, diabetic patients with anemia require higher costs to be managed (Javanbakht *et. al*., 2011; Azmi *et. al*., 2018). In addition, diabetes mellitus has an impact on the economy by decreasing the employment rate of men diagnosed with diabetes (Seuring *et. al*., 2015). In a study in Kuala Terengganu, unemployment has been a major contributor to atrocious blood glucose levels, apart from social support and belief where diabetes interferes with daily activities (Mat H. *et. al*., 2019). In addition, metabolic disorder also has a psychological impact on its patients (Jones *et. al*., 2016). Diabetes patients in Malaysia are two times likely to have been diagnosed with anxiety and depression. Anxiety was associated with age, ethnicity and ischaemic heart disease, while depression is significantly associated with age, ethnicity and household income (Ganasegeran *et. al*., 2014).

1.2 Statement of Problem

As for now, there is no record of an absolute cure for diabetes mellitus. Metformin was prescribed as a first-line oral drug to reduce hyperglycaemia through its ability to absorb glucose through the AMPK pathway (Zhou *et. al*., 2001). If metformin has not been used to control satisfactory blood glucose levels, a combination of other drugs has been prescribed for diabetic patients to control blood glucose levels (Charbonnel *et. al*., 2006). The combination of drugs is usually effective compared to initial monotherapy (Tosi *et. al*., 2003). For example, when combined with metformin, glimepiride will give better results in blood glucose levels, as this drug has been acting faster to control glycaemic levels (Umpierrez *et. al*., 2006). However, the most common combination of two or more drugs causes various adverse reactions (Bennett *et. al*., 2011). For example, sulphonylureas, an add-on drug to metformin therapy, increases the risk of cardiovascular disease in diabetic patients (Phung *et. al*., 2013). Several drugs have also been reported to have an adverse effect on older patients (Kahn *et. al*., 2006). The drugs included glybenclamide or also known as glyburide and tolbutamide. Glybenclamide in combination with metformin increases the mortality rate compared to drug monotherapy (Fisman *et. al*., 2001). While tolbutamide has led to a deterioration in cardiovascular health (Douros *et. al*., 2017).

In addition, thiazolidinediones have been reported for bone breakage in elderly women (Mabilleau *et. al*., 2010). TZD effect in bone fracture through Erk1/2 and p38 leading to osteocyte apoptosis and activation of the glitazone receptor, leading to the upregulation of sclerostin, an inhibitor of bone formation (Mieczkowska *et. al*., 2012). Pioglitazone, another TZD drug, has increased the incidence of bladder cancer shown in the previous study in French diabetic patients (Neumann *et. al*., 2012). While rosiglitazone increases the risk of myocardial infarction, it causes a higher incidence of death in patients with cardiovascular problems (Nissen and Wolski, 2007). In addition, saxagliptin, which is a DPP-4 inhibitor, increases the risk of hospitalization due to cardiac arrest (Scirica *et. al*., 2013). In addition, a study in Malaysia has shown that diabetic patients in Malaysia have poor adherence to prescribed diabetic and self-care drugs, such as blood glucose testing (Ahmad *et. al*., 2013; Jannoo and Mamode Khan, 2019). Therefore, another alternative treatment for diabetes mellitus is needed to control blood glucose levels without adverse effects.

1.3 Justification of the Study

There are a number of alternative ways to manage diabetes and chronic diseases. Complementary and alternative medicine (CAM) has been another option for the treatment of chronic diseases. CAM can take a number of forms, including prayers, natural products, chiropractic, yoga and meditation (Barnes *et. al*., 2009). The study showed that diabetic patients have a high preference for alternative treatment (Kumar *et. al*., 2006). In fact, the patient who opts for the method still uses ordinary treatment (Donald and Egede, 2006). In the United States, complementary and alternative medicines are chosen because users feel that they have more control over their health

and that the method has improved their health (Rhee *et. al*., 2018). In addition, many users were satisfied with the impact of the method (Singh *et. al*., 2004). Apart from that, the methods also include naturopathy and homeopathy. Homeopathy is a therapeutic method that uses natural sources and is believed to improve blood glucose levels (Mourão *et. al*., 2019). In Malaysia, the use of herbal medicines is favorably accepted and the prevalence is high (Aziz and Tey, 2009). CAM has been reported to be used in patients with chronic diseases in Malaysia (Hasan *et. al*., 2009). In addition, the use of CAM is high in diabetic patients in Malaysia as a herbal medicine is thought to be safe, of good quality and an additional method for conventional treatment (Hasan *et. al*., 2011). The use of *Momordica charantia* (bitter gourd) and *Orthosiphon Stamineus, Benth* (Misai Kucing) is most common in diabetic patients in Malaysia (Ching *et. al*., 2013). *Momordica charantia* has been reported to be able to regulate blood glucose levels and increase glucose disposal in muscle cells (Ahmed *et. al*., 2004). In addition, herbal medicine capable of overcoming insulin resistance by inhibiting NF-κB and JNK pathways (Yang *et. al*., 2015). Natural compounds isolated from *Momordica charantia* have been reported to be capable of inhibiting the activity of 5-007-amylase and 5-007-glucosidase (Shivanagoudra *et. al*., 2019). The hypoglycaemic effect of *Momordica charantia* is reported due to its cucurbitan constituents and is capable of enhancing the effect of rosiglitazone, a glucose-lowering drug (Harinantenaina *et. al*., 2006; Nivitabishekam *et. al*., 2009). While *Orthosiphon Stamineus, Benth* (Misai Kucing) also had a blood glucose-reducing effect (Mohamed *et. al*., 2011) and was able to inhibit 5-007-amylase and 3-glucosidase (Mohamed *et. al*., 2012).

Ficus deltoidea is another potential herbal for diabetes mellitus. In Malaysia, the herbal plant is provincially known as Mas Cotek or Serapat Angin and has been used as a post-birth decoction plant. A study in Singapore reported that *Ficus deltoidea* leaves have been used to promote health while its fruit is used for diabetes (Siew *et. al*., 2014). In addition, it has been reported that the herbal has the ability to reduce pain, to heal wounds, to have an anti-hyperglycemic, anti-inflammatory and anti-melanogenic effect and to reduce blood pressure (Sulaiman *et. al*., 2008; Abdulla *et. al*., 2010; Adam *et. al*., 2011; Oh *et. al*., 2011; Zakaria *et. al*., 2012; Kamal *et. al*., 2019). In addition, the natural compounds responsible for the antioxidant effect of this herbal product are vitexin and isovitexin (Farsi *et. al*., 2011). In fact, vitexin and isovitexin have been isolated from the leaves of *Ficus deltoidea* and have been reported to have inhibited 5-007-glucosidase (Choo *et. al*., 2012). Four methane strains of *Ficus deltoidea* have therefore been selected to further elucidate antidiabetic mechanisms in cells.

1.4 Hypothesis of the study

It is assumed that methanolic extracts of *Ficus deltoidea* varieties have antidiabetic activities and mechanisms. Specifically, methanolic *Ficus deltoidea* extracts are capable of enhancing insulin secretion through the K_{ATP} independent pathway, enhancing glucose uptake through the PI3-Kinase pathway, increasing insulin sensitivity in insulin resistance cells and inhibiting the formation of glycated proteins.

1.5 Objectives of the Study

The main objectives of this research are to elucidate antidiabetic mechanisms by using four methanolic extracts of *Ficus deltoidea* varieties. The specific objectives are:

1. To evaluate the insulin-secreting activity of methanolic extracts of *Ficus deltoidea* varieties on β-pancreatic cells and the molecular mechanisms underlying such activity.

2. To determine the potential of extracts of *Ficus deltoidea* varieties to enhance glucose uptake into insulin targeting cells and molecular mechanisms underlying such enhancement.

3. To assess insulin-sensitizing activity of extracts of *Ficus deltoidea* varieties in adipocytes cells.

4. To determine the potential of extracts of *Ficus deltoidea* varieties to prevent diabetes complications by inhibiting the production of Advanced Glycation End Products (AGE).

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BIODATA OF STUDENT

I went for primary education in Sekolah Kebangsaan Sena, Perlis and secondary education in Sekolah Menengah Kebangsaan Derma, Perlis. I continued American Degree Foundation Program (ADFP) at International Education Centre (INTEC) Shah Alam after finished with Malaysian Certificate of Education. Then I furthered my studies to Indiana University, Bloomington for Bachelors degree in Biotechnology with minors in Chemistry. I continued with Masters Degree in Biotechnology at Universiti Teknologi Malaysia, Skudai with my research entitled "Isolation and Identification of Bacteria Capable to Utilize 2,2-Dichloropropionic Acid from Danga Bay Seawater" and I am currently working as a fellow at University Malaysia Perlis.

LIST OF PUBLICATIONS

Publications

Nurshieren Yahaya, Nur Sumirah Mohd Dom, Zainah Adam, and Muhajir Hamid, "Insulinotropic Activity of Methanolic Extracts of *Ficus deltoidea* from Seven Varieties", Evidence-Based Complementary and Alternative Medicine, vol. 2018, Article ID 3769874, 8 pages, 2018.

Nurshieren Yahaya, Nursumirah Mohd Dom, Affrida Abu Hasan, Zainah Adam, and Muhajir Hamid. "Evaluation of Glucose Uptake of Standardized Methanolic *Ficus deltoidea* Extracts from Seven Varieties in L6 Muscle Cells", Diabetes Research and Clinical Practices, 2020. **(Under review)**.

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