
**UNIVERSITI PUTRA MALAYSIA**

***IN VITRO INVESTIGATION OF ANTIDIABETIC AND ANTIGLYCATION ACTIVITIES OF METHANOLIC EXTRACT OF Ficus deltoidea Jack VARIETIES***

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By

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

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**Chair : Muhajir Hamid, PhD**
**Faculty : Biotechnology and Biomolecular Sciences**

Diabetes mellitus has been listed as one of the leading death factors in the world which associated with glucose uptake activity in the human body. Nowadays, the usage of medicinal plants for the management of diabetes mellitus has gained interest even though many antidiabetic drugs are available in the market. This could possibly be due to the limitations of these drugs such as adverse effects and poor clinical efficacy. Therefore, searching for new effective antidiabetic agents should be continued. *Ficus deltoidea (F. deltoidea)* or also known as Mas Cotek is a local medicinal plant in Malaysia that has been used as a supplement to promote health and traditionally claimed to possess antidiabetic effect. However, the scientific studies to confirm its efficacy and its possible mode of actions are still inadequate.

This study was done to authenticate the antidiabetic property of *in vitro* antihyperglycemic mechanisms evaluation of *F. deltoidea* varieties, to elucidate the potential of the plant to stimulate insulin secretion from β-pancreatic cells, to enhance glucose uptake by adipocytes and muscle cells, to screen glucose uptake inhibition activity in adipocytes and muscle cells in the presence of LY294002 (PI3-Kinase inhibitor) and ALLN (CAP inhibitor), to assess the insulin sensitizing activity in adipocytes cells and to observe the expression of PPAR-gamma, PI3 Kinase, GLUT4 and CAP gene. The inhibition of advanced glycation end products formation, protein oxidation, total phenolic contents and antioxidative effects of the plant were also monitored. The viability of cells that were used in the *in vitro* evaluation of antihyperglycemic mechanisms in the presence of *F. deltoidea* extracts was determined using MTT assay.

The viability study showed that methanolic extract of *F. deltoidea* varieties did not possess any cytotoxic effect at concentration of 100 µg/ ml and this concentration was used to measure the antidiabetic mechanism of *F. deltoidea* varieties extract in BRIN BD11 pancreatic, 3T3FF42A adipocytes and L6 myotubes cells. For insulin secretion study, *F. deltoidea* variety *intermedia* stimulated the highest insulin secretion followed by *F. deltoidea* variety *kunstleri* and *F. deltoidea* variety *trengganuensis.* The result indicated that the insulin secretory action of the extracts involved KATP channel-dependent and KATP channel-independent pathways. *F. deltoidea* variety *trengganuensis, F. deltoidea* variety *kunstleri* and *F. deltoidea* variety *intermedia* also significantly enhanced basal and insulin-mediated glucose uptake into adipocytes and muscles cells. The extracts showed either insulin-mimetic or insulin-sensitizing activity or combination of both activities during enhancing glucose uptake into these cells.

Meanwhile, the result of glucose uptake inhibition assay of the extracts demonstrated that insulin stimulated glucose uptake followed phosphatidylinositiol-3-kinase-independent (PI3K) mechanism in L6 muscle and 3T3F442A adipocytes cells. In L6 myotubes cells, the highest glucose uptake activity was observed when treated with *F. deltoidea* variety *trengganuensis* and *F. deltoidea* variety *intermedia* meanwhile in adipocytes, the highest activity was found when treated with *F. deltoidea* variety *trengganuensis.* Additionally, in gene expression study, the most upregulation of PPAR-gamma gene was expressed significantly at 24 hours with the highest in *F. deltoidea* variety *kunstleri* followed by *F. deltoidea* variety *intermedia* and *F. deltoidea* variety *trengganuensis*.

The novelty of this study is about the investigation of antiglycation properties of *F. deltoidea* varieties which significantly inhibited the formation of advanced-glycation end-products (AGEs). In conjunction with a reduction of fructosamine level, the plant extracts also increased the thiol groups level and inhibited the formation of protein carbonyl. No previous report published about the potential of *F. deltoidea* plant to inhibit the formation of AGEs. The highest antiglycation activity was observed in *F. deltoidea* variety *intermedia* which also depicted the highest phenolic content and reducing power activities. The correlation study between total phenolic content and antiglycation activity, DPPH radical scavenging activity and reducing power activity showed ($-1.0 \geq r \leq 1$), ($-1.0 \geq r \leq 1$) and ($-0.69 \geq r \leq 1.0$) respectively.

In conclusion, this study had shown that *F. deltoidea* able to reduce hyperglycemia with mechanisms such as stimulation of insulin secretion from pancreatic β-cells, enhancement of glucose uptake into adipocytes and muscle cells and effects of insulin stimulated glucose uptake is through independent type of PI3K pathway. Insulin-sensitizing activities exhibited by *F. deltoidea* varieties indicated that this plant has the ability to alleviate insulin resistance and may potentially be beneficial for the treatment of type 2 diabetes mellitus with insulin-resistance condition. Finally, the *F. deltoidea* plant extract also contained phenolic compounds, possessed antioxidant and antiglycation effects that may offer remarkable prospects for the preventive treatment of AGE-mediated diabetic complications.

Hence, *F. deltoidea* varieties may offer good therapeutic potential to reduce the complications of diabetes mellitus.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia
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**PENYIASATAN SECARA *IN VITRO* AKTIVITI ANTIDIABETIK DAN ANTIGLIKASI EKSTRAK METANOLIK PELBAGAI VARIASI *Ficus deltoidea* Jack**

Oleh

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Diabetes mellitus telah disenaraikan sebagai salah satu faktor kematian di dunia yang dikaitkan dengan aktiviti pengambilan glukosa dalam badan manusia. Pada masa kini, penggunaan tumbuhan ubatan dalam mengawal diabetes mellitus telah mendapat perhatian walaupun terdapat banyak ubat antidiabetik berada di pasaran. Ini boleh disebabkan oleh limitasi ubat-ubat yang berkaitan di mana ianya mempunyai kesan buruk dan keberkesanan klinikal yang lemah. Sehubungan itu, pencarian kepada agen antidiabetik yang berkesan perlu diteruskan. *F. deltoidea* atau dikenali juga sebagai Mas Cotek merupakan tumbuhan ubatan tempatan di Malaysia yang diambil sebagai makanan tambahan untuk kesihatan dan secara tradisional didakwa mempunyai sifat antidiabetik. Namun begitu, kajian-kajian saintifik untuk mengesahkan keberkesanan dan mod tindakan yang mungkin bagi tumbuhan tersebut masih berkurangan.

Kajian ini dilaksanakan untuk mengesahkan ciri antidiabetik bagi pelbagai variasi *F. deltoidea* melalui penentuan mekanisme antihiperglisemik secara *in-vitro*. Kajian ini untuk menjelaskan potensi tumbuhan tersebut bagi meransang rembesan insulin daripada sel beta-pankreatik, untuk meningkatkan pengambilan glukosa oleh sel adipos dan sel otot, untuk melihat aktiviti pengambilan glukosa dengan kehadiran LY294002 (perencat PI3-Kinase) dan ALLN (perencat CAP) dalam sel adipos dan sel otot, untuk menilai aktiviti pemekaan insulin dalam sel adipos dan untuk melihat pengungkapan gen PPAR-gamma, PI3 Kinase, GLUT4 dan CAP. Perencatan pembentukan produk akhir glikasi lanjutan, pengoksidaan protein dan kesan antioksida ekstrak tumbuhan juga dipantau. Keupayaan untuk hidup sel-sel yang digunakan dalam kajian mekanisme antihiperglisemik secara *in-vitro* dengan kehadiran *F. deltoidea* ditentukan menggunakan ujian MTT.

Kajian keupayaan sel untuk hidup menunjukkan bahawa ekstrak pelbagai variasi *F. deltoidea* tidak mempunyai kesan sitotoksik pada kepekatan 100 µg/ ml dan kepekatan ini digunakan untk mengukur mekanisme antidiabetik ke atas sel pankreatik BRIN BD11, sel adipos 3T3F442A dan sel otot L6 myotube. Kajian tindakan perembesan insulin menunjukkan ekstrak *F. deltoidea* variasi *intermedia* merangsang perembesan insulin tertinggi diikuti oleh *F. deltoidea* variasi *kunstleri* dan *F. deltoidea* variasi *trengganuensis.* Ini menunjukkan tindakan perembesan insulin tersebut melibatkan laluan kebergantungan-KATP dan ketidakbergantungan-KATP. *F. deltoidea* variasi *trengganuensis, F. deltoidea* variasi *kunstleri* dan *F. deltoidea* variasi *intermedia* juga dengan ketara meningkatkan pengambilan glukosa pada tahap basal dan dengan perantaraan insulin dalam sel adipos dan sel otot. Ekstrak tersebut menunjukkan sama ada aktiviti peniru insulin atau pemekaan insulin atau gabungan kedua-dua aktiviti semasa meningkatkan pengambilan glukosa ke dalam sel-sel terlibat.

Sementara itu, hasil ujian perencatan pengambilan glukosa oleh *F. deltoidea* variasi *trengganuensis, F. deltoidea* variasi *kunstleri* and *F. deltoidea* variasi *intermedia* menunjukkan bahawa pengambilan glukosa yang dirangsang oleh insulin adalah sebahagiannya mengikuti mekanisma PI3-kinase-ketidakbergantungan pada sel otot L6 dan sel adipos 3T3F442A. Pada L6 myotubes, aktiviti penambahan glukosa tertinggi boleh dilihat apabila sel dirawat dengan *F. deltoidea* variasi *trengganuensis* dan *F. deltoidea* variasi *intermedia* manakala pada sel adipos, aktiviti tertinggi apabila sel dirawat dengan ekstrak *F. deltoidea* variasi *trengganuensis.* Sebagai tambahan, kajian pengungkapan gen menunjukkan bahawa peningkatan aktiviti pengambilan glukosa melalui pengungkapan gen PPAR-gamma adalah signifikan selepas 24 jam dengan pengungkapan tertinggi pada ekstrak *F. deltoidea* variasi *kunstleri* diikuti dengan *F. deltoidea* variasi *intermedia* dan *F. deltoidea* variasi *trengganuensis.*

Kebaharuan bagi kajian ini adalah mengenai sifat antiglikasi bagi pelbagai variasi *F. deltoidea* dalam merencat pembentukan produk akhir glikasi lanjutan. Kajian juga menunjukkan ekstrak tumbuhan menurunkan tahap fruktosamin, meningkatkan tahap kumpulan *thiol* dan menghalang pembentukan protein karbonil. Sehingga kini, tiada laporan direkodkan mengenai potensi tumbuhan *F. deltoidea* untuk merencatkan pembentukan produk akhir glikasi lanjutan. Aktiviti antiglikasi tertinggi dilihat pada *F. deltoidea* variasi *intermedia* yang mana ia juga menunjukan kandungan fenolik tertinggi dan aktiviti daya pengurangan. Kajian korelasi antara keseluruhan kandungan fenolik dan aktiviti antiglikasi, aktiviti pengambilan radikal DPPH dan aktiviti daya pengurangan menunjukkan ($-1.0 \geq r \leq 1$), ($-1.0 \geq r \leq 1$) dan ($-0.69 \geq r \leq 1.0$) masing-masing.

Sebagai kesimpulan, kajian ini telah menunjukkan bahawa *F. deltoidea* mempunyai kemampuan untuk mengurangkan hiperglisemia dengan mekanisme seperti merangsang perembesan insulin dari sel-sel pankreas, peningkatan pengambilan glukosa ke dalam sel adipos dan sel otot serta pengambilan glukosa yang dirangsang oleh insulin mengikut laluan PI3-kinase-ketidakbergantungan. Kegiatan pemekaan insulin oleh *F. deltoidea* menunjukkan bahawa tumbuhan ini mempunyai keupayaan untuk

mengurangkan ketahanan insulin dan berpotensi memberi manfaat untuk rawatan diabetes mellitus jenis 2 dengan keadaan ketahanan insulin. Akhirnya, ekstrak tumbuhan *F. deltoidea* juga mengandungi sebatian fenolik, mempunyai kesan antioksida dan antiglikasi yang menawarkan potensi yang bagus untuk rawatan pencegahan komplikasi diabetes yang disebabkan oleh produk akhir glikasi lanjutan. Oleh itu, pelbagai variasi *F. deltoidea* boleh menawarkan potensi terapi yang baik untuk mengurangkan komplikasi diabetes mellitus.

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| | |
|---|---|
| ADP | Adenosine diphosphate |
| AGEs | Advanced Glycation Endproducts |
| AKT | Protein Kinase B |
| ALLN | N-acetyl-Leu-Leu-Norleu-al |
| AMPK | Adenosine 5′ Monophosphate-activated Protein Kinase |
| ANOVA | Analysis of Variance |
| ATP | Adenosine Triphosphate |
| B40 | Bottom 40% households |
| cAMP | Cyclic Adenosine Monophosphate |
| CAP | Catabolite Activator Protein |
| 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 |
| HbA1c | Glycated haemoglobin |
| IFN-γ | Interferon-gamma |
| IL-6 | Interleukin 6 |

| | |
|---|---|
| *IL-1β* | *Interleukin 1* beta |
| IRS-1 | Insulin receptor Substrate 1 |
| JNK | c-Jun NH2-terminal kinase |
| $K_{ATP}$ | ATP-sensitive potassium |
| KRB | Kreb's Ringer Buffer |
| MAPK | Mitogen-Activated Protein Kinase |
| MODY | Maturity onset of diabetes in youth |
| 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 |
| SUs | Sulfonylureas |
| TNF-α | Tumor Necrosis Factor Alpha |
| TZDs | Thiazolidinediones |

# CHAPTER 1

# INTRODUCTION

## 1.1 Background of Study

Diabetes mellitus is a chronic metabolic disease characterized by hyperglycemia due to the deficiency in either insulin secretion or insulin action or by combination of both factors. Diabetes mellitus is the seventh leading death factor in the world and has caused 1 million mortalities in 2000 and increased to 1.6 million in 2016 (WHO, 2018). The same report discovered that 422 million people around the world suffered from diabetes, mainly in middle- and poor-income countries. It is also stated that over the years, more patients experienced with diabetes and become more predominance. In India, around 41 million people were diagnosed with diabetic and expected to escalate to 70 million in 2025 (Sicree *et al.,* 2006). Skyler *et al.,* (2017) reported that more diabetic adults originated from East Asia, South Asia and Australia compared to other regions with a total of 153 million patients.

Institute for Public Health (2020) has conducted a National Health and Morbidity Survey (NHMS) among Malaysian and discovered a prevalence rate of diabetes in adults was 13.4% in 2015 and increased to 18.3% in 2019. The highest prevalence of diabetes was recorded among Indians (31.4%), followed by Malays (21.6%), Chinese (15.1%), and Bumiputera Sarawak (12.3%). The report also classified the disease was more common among widow(er)/ divorcee (33.2%), patient with no formal education (28.7%), retirees (45.8%) and people with low socio-economic (B40) group (18.5%). The predominance of diabetes in the urban area was depicted at 9.7%, not much different to rural area at 8.2%. However, when compared between states, the highest prevalence was found in Perak (15.2%) followed by Melaka (13.7%), Perlis (13.5%), Sabah (4.1%) and Sarawak (7.7%) respectively with no record mentioned on other states in Malaysia (Institute for Public Health, 2020). In conjunction, it was stated that the development of T2DM is associated with low socio-economic conditions such as occupational rank, educational status and income level (Agardh *et al.,* 2011).

The NHMS 2019 survey also found that around 3.9 million Malaysians are suffering from diabetes. The figure depicted as the highest rate in Asia and resembled among the highest in the world (Institute for Public Health, 2020). Meanwhile, around 8.1% of the adult population in Malaysia, or similar to 1.7 million people, possessed high possibilities to suffer from diabetes, hypertension, and high cholesterol diseases. They also projected that by 2025, 7 million Malaysian adults are likely to suffer from diabetes which encounter for 31.3% diabetes prevalence for adults aged 18 years and above. The same report mentioned a ratio of 1:5 adults aged 18 years and above are suffering from

diabetes and the trend of prevalence has increased from 7.2% (2011) followed by 8.3% (2015) and steadily increased to 9.4% (2019) which have been diagnosed with diabetes meanwhile, 4.0% (2011), 5.1% (2015) and 8.9% (2019) of adults claimed that they did not realize they have diabetes (Institute for Public Health, 2020).

Environmental factors such as obesity, in-active lifestyles, aging, daily intake containing processed food, hereditary factors, and epigenetic modifications responsible to the increasing of diabetes cases (Ma *et al.,* 2014). Other than focused on the lifestyle interventions, intake of oral medications, injection of insulin and other treatment based on pharmacogenomic, proteomic, and metabolomic approaches could help in fight against diabetes mellitus (Hu and Jia, 2018). From the data of Adult Diabetes Control and Management (ADCM) of Malaysia, the usage of insulin injection has recorded 12.9% and 85.6% were prescribed with anti-hyperglycemic agents such as biguanides (83.2%) and sulfonylureas (69.9%). Other than that, the diabetic patients were prescribed with angiotensin-converting enzyme inhibitors (63.9%) and calcium channel blockers (<40%), meanwhile, about 58.2% were on antihypertensive agent treatment (Mastura *et al.,* 2011).

## 1.2 Statement of Problem

The ultimate mission for diabetes treatment is to reduce and maintain glycated hemoglobin (HbA1c) level below 7%. Higher HbA1c levels (7.0% and above) can progress to macrovascular and microvascular complications. The macrovascular complications are known as cardiovascular, cerebrovascular, and peripheral vascular disease meanwhile, microvascular risks are identified as nephropathy, neuropathy, and retinopathy complications (Stein *et al.,* 2013; He *et al.,* 2015). Therefore, to maintain normal blood glucose levels and minimize the complications of diabetes, the usage of oral antidiabetic drugs has been approved by Drug Administration or European Medicines Agency (He *et al.,* 2015).

Currently, several oral synthetic antidiabetic drugs have been used to treat the disease but have displayed undesirable side effects. Metformin is the first choice of oral medication to diabetic's patients followed by second-line prescription of sodium-glucose co-transporter-2 (SGLT-2) inhibitors, thiazolidinediones (TZDs), sulfonylureas (SUs), dipeptidyl peptidase 4 (DPP-4) inhibitors, alpha-glucosidase inhibitors (AGIs), and meglitinides (Qian *et al.,* 2018). The adverse effects of metformin are known as risk of getting neuropathy in elderly, may cause anemia, mild weight loss, and nausea/ vomiting or diarrhea; meanwhile for DPP-4 inhibitors (inflammation of pancreas and upper respiratory tract infection); SGLT-2 inhibitors (bone fractures, genital mycosis and may increase low-density lipoprotein cholesterol); sulfonylureas (weight gain and increase cardiovascular disease risk); and TZDs (weight gain, cardiac failure, risk of liver disease, anemia risk, swelling of legs or ankles) (Chaudhury *et al.,* 2017). Other than that, meglitinides and alpha-glucosidase inhibitors are not frequently

prescribed as both drugs require multiple divided dosage and develop inefficient treatment (Hussein *et al.,* 2015). In addition, referring to NHMS 2019 report, about 25.7% of diabetes patients claimed that they were on insulin therapy, 85.6% were prescribed with oral antidiabetic drugs within the past 2 weeks, meanwhile 88.0% had a diabetes diet advice from healthcare staffs. Another 75.4% were advised to lose some weight and 23.0% had shifted to traditional and complementary medicines (Institute for Public Health, 2020).

Therefore, searching for alternative and advanced solution for diabetes mellitus are favorable and urgently needed. In recent years, many group of researchers had focused on research using plant-based products to treat various diseases including diabetes mellitus (Abbas *et al.,* 2019). The safety aspects in the use of oral antidiabetic drugs should be considered and limitations of the antidiabetic drugs such as the undesirable side effects, lack of clinical efficacy and inconsistent effects of the antidiabetics drugs on each patient need to be further studied.

### 1.3 Justification of the Study

Even though no specific cure has been found for diabetes mellitus yet, there are many ways to overcome the disease. Aside from oral antidiabetic drugs (conventional medicine), there are complementary and alternative medicine (CAM) therapies suggested for diabetes which refers to other method of healing treatment. In the meantime, National Center for Complementary and Integrative Health (NCCIH), National Institute of Health, defined complementary medicine as other practice that paired together with conventional medicine meanwhile alternative medicine as other routine that used in place of conventional medicine (NCCIH, 2018). In addition, WHO has estimated for the total world population, around 80% are using complementary and alternative medicine for their basic wellness (Yang *et al.,* 2015). The report also outlined the complementary and alternative medicine therapies such as dietary supplement from natural products (herbs), mind and body practices (yoga, chiropractic, acupuncture), Ayurvedic medicine, traditional Chinese medicine, homeopathy and naturopathy. Additionally, another recent term introduced is integrative health care which refers to combination of conventional and complementary approaches together in a coordinated way (NCCIH, 2018).

In traditional practices, various medicinal plants have been utilized to forbid long term complications in diabetes because of low cost, easy to find and less adverse effects (Deepa *et al.,* 2018). It was recorded that around 200 bioactive compounds consist of phenolic acids, flavonoids, triterpenoids, alkaloids and carbohydrates have been isolated from therapeutic plants and possessed antidiabetic effects (Misbah *et. al.,* 2013). A review report by Birdee *et al*., (2010) listed some plants that have been used to treat diabetes for instance *Allium sativum*, Aloe vera and *Gymnema sylvestre*, which have insulin secretagogue effects. In addition, *Coccinia indica* has insulin mimetic effect, *Momordica charantia* possessed insulin mimetic effect and decreased hepatic glucose

production, meanwhile *Trigonella foenum graecum* acts as insulin secretagogue and decreased carbohydrate absorption. Apart from that, a plant called *Opuntia streptacantha* decreased carbohydrate absorption and lastly *Panex ginseng, P. quiquefolius* works as insulin mimetic and alters the hepatic glucose metabolism.

Other than that, *Ficus deltoidea* (*F. deltoidea)* or local folks addressed it as Mas Cotek is one of the medicinal plants which possessed antidiabetic properties but not extensively been studied yet. *F. deltoidea* is a shrub tree from Moraceae family which is primarily cultivated and can be found in Peninsular Malaysia, Java, Thailand, Borneo, Sumatra and Moluccas (Berg *et al.,* 2005). In Malaysia, this plant has been used as an alternative treatment and has been reported for antidiabetic, antinociceptive, antiulcer, antioxidant, anti-inflammatory as well as anti-melanogenic properties (Misbah *et al.,* 2013). Meanwhile, *in vivo* study showed that oral intake of ethanolic extract of *F. deltoidea* leaves significantly reduced the blood glucose level in the diabetic rats (Mohammad Noor *et al.*, 2016). Previous research by Adam *et al.* (2012) reported on *in vivo* and *in vitro* antidiabetic study of *F. deltoidea* extract but not specific for each variety and the mechanism involved. Nevertheless, extensive study on antidiabetics mechanisms and efficiency of *F. deltoidea* plant in inhibiting diabetes risk factor is still incomplete and need further research.

## 1.4 Objectives of the Study

The main objective of this study is to elucidate the antidiabetic mechanisms of three varieties of methanolic *F. deltoidea* extracts using *in vitro* models. The specific objectives of the study are:

1. To evaluate insulin secreting activity of β-pancreatic cells treated with methanolic extracts of *F. deltoidea* varieties and the molecular mechanisms underlies such activity.

2. To determine the potential of methanolic extracts of *F. deltoidea* varieties to enhance glucose uptake into insulin-targeting cells and molecular mechanisms underlies such activity.

3. To evaluate insulin sensitizing activity of adipocytes cells treated with methanolic extracts of *F. deltoidea* varieties.

4. To determine the potential of methanolic extracts of *F. deltoidea* varieties towards inhibition of advanced glycation end products formation, total phenolic content and antioxidative properties.

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