ANTI-DIABETES MECHANISM OF ACTION BY SYNACINN™ IN ADIPOCYTES

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"Verily after every difficulty, there's a relief" (Surah Al-Inshirah)

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ABSTRACT

Type 2 diabetes mellitus is described as a defective action of insulin to properly regulate glucose transport within cells and clinically known as insulin resistance. Several factors such as elevated free fatty acid, glucocorticoids as well as abnormal levels of cytokines have been reported to cause insulin resistance. Potentially, phytochemical agents with insulin resistance reverting effect could serve as an alternative treatment for type 2 diabetes mellitus. Synacinn™ is a polyherbal supplement formulated from *Andrographis paniculata, Curcuma xanthorrhiza, Cinnamomum zeylanicum, Eugenia polyantha* and *Orthosiphon stamineous*. It is claimed as a hypoglycemic agent for diabetes mellitus treatment. Even though the anti-diabetes potential of each singular herbs has been well examined, scientific evidence has never been reported for polyherbal combination. In this study, the potential anti-diabetes mechanism of standardized Syancinn™ was investigated using two types of *in vitro* models; normal and insulin-resistant 3T3-L1 adipocytes. It was found that Synacinn™ improved the insulin-mediated glucose utilization in both models. For normal adipocytes, the increase of glucose utilization resulted in overexpression of glucose transporter 4, insulin receptor 1 and protein kinase B. Meanwhile in insulin resistant adipocytes, Synacinn™ increased the glucose transporter 4 expression without affecting the insulin receptor 1 and protein kinase B expression, indicating that Synacinn™ mechanism of action is dominant on the glucose transport rather than repairing the insulin signal transduction. This study also shows that Synacinn™ is a mild peroxisome proliferator-activated receptor gamma ligand and pro-adipogenic agent. During adipogenesis, Synacinn™ stimulated the peroxisome proliferator-activated receptor gamma nuclear transcriptional activity, as well as expression of (cytosine-cytosine-adenosine-adenosine-thymidine)-enhancer-binding protein alpha, adiponectin, glucose transporter 4 and protein kinase B. In terms of safety, standardized Syancinn™ was free from heavy metals and microbial contaminations and the concentrations used in the experiment do not affect the normal embryogenesis of zebrafish. Collectively, results suggest that Synacinn™ is a peroxisome proliferator-activated receptor gamma ligand agent which acted through two mechanisms: 1) restores the insulin-mediated glucose utilization by activating the glucose transporter 4 expression in insulin resistant adipocytes and 2) enhances the adipogenesis into insulin-sensitive adipocytes containing abundance of glucose transporter 4 resulted from activation of (cytosine-cytosine-adenosine-adenosine-thymidine)-enhancer-binding protein alpha and proliferator-activated receptor gamma.

ABSTRAK

Diabetes mellitus jenis 2 digambarkan sebagai kecacatan terhadap tindak balas insulin untuk mengawal pengangkutan glukosa di antara sel dan secara klinikal dikenali sebagai rintangan terhadap insulin. Beberapa faktor seperti peningkatan asid lemak bebas, glukokortikoid serta tahap sitokin yang tidak normal telah dilapor menyebabkan rintangan terhadap insulin. Agen fitokimia dengan potensi berbalik terhadap kesan rintangan ke atas insulin mampu dijadikan rawatan alternatif terutamanya untuk diabetes mellitus jenis 2. Synacinn™ adalah suplemen pelbagai herba yang diformulasikan dari *Andrographis paniculata, Curcuma xanthorrhiza, Cinnamomum zeylanicum, Eugenia polyantha* dan *Orthosiphon stamineous*. Ia dikatakan sebagai agen hipoglisemik untuk rawatan diabetes mellitus. Walaupun potensi anti-diabetes untuk setiap herba telah pun dikaji dengan terperinci, akan tetapi, tiada laporan saintifik yang telah diterbitkan dalam bentuk gabungan pelbagai herba. Dalam kajian ini, potensi mekanisma anti-diabetes bagi Synacinn™ yang telah dipiawaikan, diselidik menggunakan dua jenis model *in vitro*; sel lemak normal dan sel lemak yang rintang terhadap insulin (3T3-L1). Kajian mendapati bahawa, Synacinn™ menambah baik penggunaan glukosa yang didorong oleh insulin di dalam kedua-dua model. Bagi sel lemak normal, penigkatan penggunaan glukosa menyebabkan ekspresi lebihan pada pengangkut glukosa 4, reseptor insulin 1 dan kinase protein B. Manakala bagi sel lemak yang rintang terhadap insulin, Syancinn™ meningkatkan ekspresi pengangkut glukosa 4 tanpa mempengaruhi reseptor insulin 1 dan kinase protein B dan ini menunjukkan bahawa mekanisme tindakan bagi Synacinn™ adalah dominan pada pengangkutan glukosa dan bukannya pada memperbaiki transduksi isyarat insulin. Kajian juga menunjukkan bahawa Synacinn™ adalah ligan reseptor pengaktifan proliferator peroksisom gamma yang sederhana dan agen pro-adipogenik. Semasa *adipogenesis*, Synacinn™ merangsang aktiviti transkripsi reseptor pengaktifan proliferator peroksisom gamma nukleus, serta ekspresi protein penggalak ikatan alfa (sitosina-sitosina-adenosina-adenosina-timidina), adiponektin, pengangkut glukosa 4 dan kinase protein B. Dari segi keselamatan, Syancinn™ yang telah dipiawaikan ini adalah bebas daripada pencemaran logam berat dan mikrob dan kepekatan yang digunakan dalam eksperimen tidak mempengaruhi embriogenesis normal zebrafish. Secara keseluruhannya, keputusan menunjukkan bahawa Synacinn™ adalah agen ligan reseptor pengaktifan proliferator peroksisom gamma yang bertindak melalui dua mekanisma: 1) mengembalikan penggunaan glukosa yang didorong oleh insulin dengan mengaktifkan ekspresi pengangkut glukosa 4 didalam sel lemak yang rintang terhadap insulin dan 2) meningkatkan *adipogenesis* kepada sel lemak yang sensitif terhadap insulin yang mana mengandungi limpahan pengangkut glukosa 4 hasil daripada pengaktifan protein penggalak ikatan alfa (sitosina-sitosina-adenosina-adenosina-timidina) dan reseptor pengaktifan proliferator peroksisom gamma.

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AKT/ PKB	Protein kinase B
AP	*Andrographis paniculata*
AS160	Akt substrate of 160 kDa
aPKC	Atypical protein kinase C
ATCC	American Type Culture Collection
ATP	Adenosine triphosphate
BSA	Bovine serum albumin
C/EBPα	CCAAT-enhancer-binding protein alpha
C/EBPβ	CCAAT-enhancer-binding protein beta
C/EBPδ	CCAAT-enhancer-binding protein delta
CCAAT	Cytosine-cytosine-adenosine-adenosine-thymidine
CD1	Complete DMEM 1
CD2	Complete DMEM 2
CX	*Curcuma xanthorrhiza*
CZ	*Cinnamomum zeylanicum*
DEX	Dexamethasone
DM	Diabetes mellitus
DM1	Differentiation media 1
DM2	Differentiation media 2
DMEM	Dulbecco's Modified Eagle's Medium
DMSO	Dimethyl sulfoxide
EP	*Eugenia polyantha*
FFA	Free fatty acid
FBS	Fetal bocine serum
FCS	Fetal calf serum
FTIR	Fourier Transmission Infra-Red spectroscopy
GCs	Glucocorticoids
GSV	Glucose transporter storage vasicle

GC-MS	Gas chromatography-mass spectrometry
GLUT2	Glucose transporter 2
GLUT4	Glucose transporter 4
G6P	Glucose-6-phosphatase
HBA1C	Hemoglobin A1C
hpf	Hour post fertilization
IBMX	Methylisobutylxanthine
INS	Insulin
IL-6	Interleukin -6
IRs	Insulin receptors
IRS1	Insulin receptor 1
IRS2	Insulin receptor 2
HPLC	High performances liquid chromatograhpy
KLFs	Kruppel-like Factors
LDL	Low density lipid
MTT	3-(4,5- dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
MAPKinases	Mitogen-activated protein kinase
NAFLD	Nonalcoholic fatty liver disease
NF-κB	Nuclear factor-kappaB
NIDDM	Non-insulin-dependent diabetes mellitus
ORO	Oil red O
OS	*Orthosiphon stamineous*
p38MAPK	P38 mitogen-activated protein kinases
PAI-1	Plasminogen activator inhibitor-1
PBS	Phosphate-Buffered Saline
PDK1	Pyruvate dehydrogenase kinase 1
PDK2	mTOR-RICTOR
PFA	Paraformaldehyde
PI3K	Phosphatidylinositol 3-kinase
PIP2	3'-phosphatidylinositol 3,4,5-bisphopsphate
PIP3	3'-phosphatidylinositol 3,4,5-trisphopsphate
PS	Penicillin strep
PPAR-γ	Peroxisome proliferator-activated receptor gamma

PTP1B	Protein tyrosine phosphatase 1B
ROS	Rosiglitazone
SGK	Glucocorticoid-inducible kinase
SREBP-1	Sterol regulatory element-binding protein 1
TBS	Tris Buffer Saline
TBST	Tris Buffer Saline – Tween 20
TCM	Traditional Chinese Medicine
TNF-α	Tumor necrosis factor α
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TZDs	Thiazolidinediones
WI	With insulin
WO	Without insulin

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CHAPTER 1

INTRODUCTION

1.1 Background of the Study

Diabetes mellitus (DM) is a metabolic disorder disease. The condition of DM is clinically diagnosed by the high level of glucose in circulating blood and known as hyperglycemia. It is triggered by insufficient and ineffective insulin actions in regulating blood glucose properly. The high glucose level affects several important body metabolisms including glucose, proteins and triglyceride metabolism which cause kidney and renal failure, heart and cardiovascular disease, blindness and nerves degeneration (Katiyar *et al.*, 2015). Clinical investigations have identified several factors linked to DM such as autoimmune reactions, hereditary factors, unhealthy diet, lack of exercises and overweight. Approximately, 17.5% of Malaysian adults above 18 years old were affected by DM in 2015 and the highest among Asian countries (Hanum, 2017). In fact, 9.2% of DM patients are unaware of their hidden disease (Hanum, 2017). This large-scale epidemic has cost millions of lives worldwide and billion dollars for treatments. In Malaysia, our government has to spend RM 2684.24 per diabetic patient, while each patient with kidney failure needs RM 1400 to RM 3200 monthly for hemodialysis (Hanum, 2017).

DM is categorized into two main groups as clinically manifested. Type 1 diabetes mellitus (T1DM) or juvenile diabetes is an autoimmune destruction and dysfunction of pancreatic beta cells, a specialized cell for insulin production. Patients with this type of DM require external insulin injection due to insulin insufficiency. Meanwhile for Type 2 diabetes mellitus (T2DM), which comprises 9/10 of total DM

patients, usually occurs in adults and clinically diagnosed by a high level of blood glucose and hemoglobin A1C (HBA1C). However, a recent report had found an increasing trend of T2DM among young ages in Japan and USA (Alberti *et al.*, 2004).

High level of blood glucose in T2DM is caused by the ineffective cellular response towards the insulin action. This phenomenon is known as insulin resistance. It occurs mainly in insulin-sensitive tissues such as liver, muscles and adipose. In insulin resistance cells, it was reported that the defective insulin signaling pathway blocked the phosphorylation signals at various steps which subsequently reduced the translocation of glucose transporters (Saini, 2010). One of the factors that induced the insulin resistance occurrence is glucocorticoids (GCs). GCs such as dexamethasone, cortisol and cortisone are clinically used to treat a range of human diseases including autoimmune diseases, cancer as well as prevention agent in organ transplantation from rejection (Ferris and Kahn, 2012). However, circulated GCs in body system also increases the adiposity and enhance the lipolysis, leading to elevate of free fatty acid (FFA) and insulin resistance (Lee et al., 2014; Rhee et al., 2004). In *in vitro* models, DEX-induced insulin resistance in adipocytes and muscles cells. It was observed that DEX inhibited the activity of downstream cytokines in the insulin signaling pathway including phosphatidylinositol 3-kinase (PI3K), protein kinase B (AKT), Akt substrate of 160 kDa (AS160) and glucose transporter 4 (GLUT4) (Tappy *et al.*, 1994).

Thiazolidinediones (TZDs), an oral anti-diabetes drug class has shown to reduce the insulin resistance effect by sensitizing the insulin activity during glucose uptake (Arner, 2003). Rosiglitazone and pioglitazone are the examples of TZDs drug available in the market. In adipocytes, TZDs acted as peroxisome proliferator-activated receptor gamma (PPARγ) ligand agent which stimulates the transcription of various genes including IRS1, GLUT4, CCAAT-enhancer-binding protein (C/EBPs), AKT, PI3K and adiponectin (Cuzzocrea *et al.*, 2004). On other aspects, TZDs also enhances the adipogenesis process (Hausman *et al.*, 2008). Adipogenesis is a differentiation process of preadipocytes to mature adipocytes which involves changes in cells phenotypes and genotypes regulation (Lowe *et al.*, 2011). Replacement of

enlarging and inflamed adipocytes with small adipocytes has been proposed as an alternative method for obesity and anti-diabetes treatment (Müller, 2011).

In search of DM therapeutic drugs, plant derives products have shown exciting potential as hypoglycemic agents. In Malaysia, herbal products have become the popular alternative for health-promoting supplement with annual income approximately RM 17 billion in 2013 and increasing 8-15% each year (Embong, 2007; Zakaria, 2015). Traditional medicine such as Traditional Chinese Medicine (TCM), Ayurvedic and Campa are prepared in a polyherbal mixture containing several herbs, spices and plants to enhance the bioactive effectiveness as well as eliminate undesired adverse events (Katiyar *et al.*, 2015; Yeo *et al.*, 2011). There are various polyherbal formulations have been developed to treat DM including Diabe Diabet, Diabecon, Diabeta, Diakyur, Diasulin, Dihar Dihar, DRF/AY/5001, ESF/AY/500, 5EPHF, Karmin Plus, Okudiabet, PM021 (Katiyar *et al.*, 2015).

1.2 Problem Statement

Despite the advanced research in drugs development, DM therapies require lifelong drugs consumption to control the glycemic condition at a normal level. Various oral therapeutic drugs for T2DM are available in market such as metformin, sulphonylureas, and alpha-glucosidase inhibitors with a specific mechanism of action and site of action (Moller, 2001). Unfortunately, these drugs have limitations and unwanted side effects (Chaudhury *et al.*, 2017; Kumar *et al.*, 2016). For example, metformin increases glucose uptake in body tissues and inhibits gluconeogenesis in liver but it is an appetite suppressant and not suitable for patients with liver and kidney problems (The Diabetes Prevention Program Research, 2012). Meanwhile for sulphonylureas, an insulin release stimulator, only suitable for T2DM patients (Kalra *et al.*, 2015). Potentially, natural therapies derived from plants (single compounds, a group of compounds or whole extract) have become an alternative choice to reduce and prevent DM traditionally (Katiyar *et al.*, 2015; Prabhakar and Doble, 2011).

Synacinn™, a traditional supplement has been recommended for treatment of DM. Its testimonials claimed to reduce DM related signs including tiredness and high blood glucose level. Synacinn™ is formulated from a combination of five Malaysian herbs including *Andrographis paniculata, Curcuma xanthorrhiza, Cinnamomum zeylanicum, Eugenia polyantha* and *Orthosiphon stamineous*. Even though there are various reports regarding the anti-diabetes potential of each single herbs, but there is no scientific reports have been published for polyherbal combination. It is believed that the synergistic effect of this combination involved multiple mechanisms ultimately covering all possible effects of DM in our body. Hence, the recent challenge is to identify and understand the mechanism of action of Synacinn™ at cellular levels in treating DM. Insulin-sensitive 3T3-L1 adipocytes were employed as DM *in vitro* model due to the important roles on glucose metabolism and insulin signaling pathway.

1.3 Research Questions

To accomplish the proposed study, several questions need to be answered:

i. What are the concentrations of phytochemicals in Synacinn™?
ii. How Synacinn™ reduces the insulin resistance effect?
iii. Does Synacinn™ produce similar effect as PPARγ ligand on the development of adipocytes?

1.4 Objectives of the Study

i. To establish the quality control and safety endpoints of Synacinn™.
ii. To evaluate the possible anti-diabetes mechanism of Synacinn™ on insulin-resistance 3T3-L1 adipocytes specifically for the glucose transport and insulin signaling pathway.
iii. To investigate PPARγ ligand activity on the development of adipocytes.

1.5 Scopes of the Study

Herbal product is composed of multiple bioactive compounds which act synergistically to improve human health. Poor quality control (QC) especially on the raw materials and the manufacturing process will result in variation between batches and possible contamination from hazardous compounds, microbes and heavy metals. Hence, strict QC is imperative to control and standardize the herbal-based production. 3T3-L1 preadipocytes can be differentiated to adipocytes by suitable hormones. Once differentiated, it is sensitive to insulin and play important role in insulin pathway and glucose metabolism (Gregoire *et al.*, 1998; Medina-Gomez *et al.*, 2007; Ntambi and Young-Cheul, 2000). Several scopes were identified based on the Synacinn™ QC aspects as well as adipocytes capability in order to achieve the proposed objectives.

i. Quality control of phytochemicals in the water extract of Synacinn™ using Fourier Transmission Infra-Red Spectroscopy (FTIR), Gas Chromatography – Mass Spectroscopy (GC-MS) and High Performance Liquid Chromatography (HPLC).
ii. Adipocytes were treated with dexamethasone to induce insulin resistance condition. Synacinn™ effect on this model is assessed based on the glucose utilization capacity and the restoration of impaired insulin signaling pathway.
iii. Adipogenesis of 3T3-L1 preadipocytes can be induced by chemical cocktail. The modulation effect of Synacinn™ on the adipogenesis was measured by quantifying the lipid droplet formation, intracellular triglyceride and adipokines expression using immunoblotting and transcription assay.

1.6 Significance of the Study

1. Provides the first possible mechanism of action of Synacinn™ for a better understanding on how it works as anti-diabetes supplement.
2. Leads to further preclinical and clinical tests on higher models.

REFERENCES

Afandi, B., Toumeh, M. S., and Saadi, H. F. (2003). Cushing's syndrome caused by unsupervised use of ocular glucocorticoids. *Endocr Pract, 9*(6), 526-529.

Aggarwal, B. B. (2010). Targeting inflammation-induced obesity and metabolic diseases by curcumin and other nutraceuticals. *Annu Rev Nutr, 30*, 173-199.

Akbar, S. (2011). Andrographis paniculata: a review of pharmacological activities and clinical effects. *Altern Med Rev, 16*(1), 66-77.

Al-Suede, F. S. R., Khadeer Ahamed, M. B., Abdul Majid, A. S., Baharetha, H. M., Hassan, L. E. A., Kadir, M. O. A., et al. (2014). Optimization of Cat's Whiskers Tea (Orthosiphon stamineus) Using Supercritical Carbon Dioxide and Selective Chemotherapeutic Potential against Prostate Cancer Cells. *Evidence-Based Complementary and Alternative Medicine, 2014*, 15.

Alberti, G., Zimmet, P., Shaw, J., Bloomgarden, Z., Kaufman, F., and Silink, M. (2004). Type 2 Diabetes in the Young: The Evolving Epidemic. *The International Diabetes Federation Consensus Workshop, 27*(7), 1798-1811.

Alessi, M. C., Poggi, M., and Juhan-Vague, I. (2007). Plasminogen activator inhibitor-1, adipose tissue and insulin resistance. *Curr Opin Lipidol, 18*(3), 240-245.

Alshawsh, M. A., Abdulla, M. A., Ismail, S., and Amin, Z. A. (2011). Hepatoprotective Effects of Orthosiphon stamineus Extract on Thioacetamide-Induced Liver Cirrhosis in Rats. *Evidence-Based Complementary and Alternative Medicine, 2011*, 6.

Amini, Z., Boyd, B., Doucet, J., Ribnicky, D. M., and Stephens, J. M. (2009). St. John's Wort inhibits adipocyte differentiation and induces insulin resistance in adipocytes. *Biochem Biophys Res Commun, 388*(1), 146-149.

Anand, P., Murali, K. Y., Tandon, V., Murthy, P. S., and Chandra, R. (2010). Insulinotropic effect of cinnamaldehyde on transcriptional regulation of pyruvate kinase, phosphoenolpyruvate carboxykinase, and GLUT4 translocation in experimental diabetic rats. *Chem Biol Interact, 186*(1), 72-81.

Aneja, D. K., Lohan, P., Arora, S., Sharma, C., Aneja, K. R., and Prakash, O. (2011). Synthesis of new pyrazolyl-2, 4-thiazolidinediones as antibacterial and antifungal agents. *Organic and Medicinal Chemistry Letters, 1*, 15-15.

Arner, P. (2003). The adipocyte in insulin resistance: key molecules and the impact of the thiazolidinediones. *Trends in Endocrinology & Metabolism, 14*(3), 137-145.

Arner, P., and Rydén, M. (2015). Fatty Acids, Obesity and Insulin Resistance.

Bardi, D. A., Halabi, M. F., Hassandarvish, P., Rouhollahi, E., Paydar, M., Moghadamtousi, S. Z., et al. (2014). Andrographis paniculata Leaf Extract Prevents Thioacetamide-Induced Liver Cirrhosis in Rats. *PLoS ONE, 9*(10), e109424.

Barthel, A., and Joost, H. G. (2008). Insulin Receptor. In S. Offermanns and W. Rosenthal (Eds.), *Encyclopedia of Molecular Pharmacology* (pp. 632-636). Berlin, Heidelberg: Springer Berlin Heidelberg.

Bevan, P. (2001). Insulin signalling. *Journal of Cell Science, 114*(8), 1429-1430.

Boden, G., and Shulman, G. I. (2002). Free fatty acids in obesity and type 2 diabetes: defining their role in the development of insulin resistance and β-cell dysfunction. *European Journal of Clinical Investigation, 32*, 14-23.

Borges, F., Roleira, F., Milhazes, N., Santana, L., and Uriarte, E. (2005). Simple coumarins and analogues in medicinal chemistry: occurrence, synthesis and biological activity. *Curr Med Chem, 12*(8), 887-916.

Bouskila, M., Pajvani, U. B., and Scherer, P. E. (2005). Adiponectin: a relevant player in PPAR[gamma]-agonist-mediated improvements in hepatic insulin sensitivity? *Int J Obes Relat Metab Disord, 29*(S1), S17-S23.

Brown, P. D., Badal, S., Morrison, S., and Ragoobirsingh, D. (2007). Acute impairment of insulin signalling by dexamethasone in primary cultured rat skeletal myocytes. *Mol Cell Biochem, 297*(1-2), 171-177.

Bubols, G. B., Vianna Dda, R., Medina-Remon, A., von Poser, G., Lamuela-Raventos, R. M., Eifler-Lima, V. L., et al. (2013). The antioxidant activity of coumarins and flavonoids. *Mini Rev Med Chem, 13*(3), 318-334.

Burén, J., Lai, Y. C., Lundgren, M., Eriksson, J. W., and Jensen, J. (2008). Insulin action and signalling in fat and muscle from dexamethasone-treated rats. *Archives of Biochemistry and Biophysics, 474*(1), 91-101.

Buren, J., Liu, H., Jensen, J., and Eriksson, J. (2002). Dexamethasone impairs insulin signalling and glucose transport by depletion of insulin receptor substrate-1, phosphatidylinositol 3-kinase and protein kinase B in primary cultured rat adipocytes. *European Journal of Endocrinology, 146*(3), 419-429.

Cao, H., Graves, D. J., and Anderson, R. A. (2010). Cinnamon extract regulates glucose transporter and insulin-signaling gene expression in mouse adipocytes. *Phytomedicine, 17*(13), 1027-1032.

Cao, Z., Umek, R. M., and McKnight, S. L. (1991). Regulated expression of three C/EBP isoforms during adipose conversion of 3T3-L1 cells. *Genes & Development, 5*(9), 1538-1552.

Cawthorn, W. P., and Sethi, J. K. (2008). TNF-α and adipocyte biology. *FEBS Letters, 582*(1), 117-131.

Cha, B. S., Ciaraldi, T. P., Carter, L., Nikoulina, S. E., Mudaliar, S., Mukherjee, R., et al. (2001). Peroxisome Proliferator-Activated Receptor (PPAR) γ and Retinoid X Receptor (RXR) agonists have complementary effects on glucose and lipid metabolism in human skeletal muscle. *Diabetologia, 44*(4), 444-452.

Chan, K. (2003). Some aspects of toxic contaminants in herbal medicines. *Chemosphere, 52*(9), 1361-1371.

Chaudhury, A., Duvoor, C., Reddy Dendi, V. S., Kraleti, S., Chada, A., Ravilla, R., et al. (2017). Clinical Review of Antidiabetic Drugs: Implications for Type 2 Diabetes Mellitus Management. *Frontiers in Endocrinology, 8*, 6.

Chen, L., Li, Q.-Y., Shi, X.-J., Mao, S.-L., and Du, Y.-L. (2013). 6-Hydroxydaidzein Enhances Adipocyte Differentiation and Glucose Uptake in 3T3-L1 Cells. *Journal of Agricultural and Food Chemistry, 61*(45), 10714-10719.

Chen, Y., Li, Y., Wang, Y., Wen, Y., and Sun, C. (2009). Berberine improves free-fatty-acid-induced insulin resistance in L6 myotubes through inhibiting peroxisome proliferator-activated receptor gamma and fatty acid transferase expressions. *Metabolism, 58*(12), 1694-1702.

Choi, S. S., Cha, B. Y., Lee, Y. S., Yonezawa, T., Teruya, T., Nagai, K., et al. (2009). Magnolol enhances adipocyte differentiation and glucose uptake in 3T3-L1 cells. *Life Sci, 84*(25-26), 908-914.

Chu, C. Y., Chen, C. F., Rajendran, R. S., Shen, C. N., Chen, T. H., and Yen, C. C. (2012). Overexpression of Akt1 enhances adipogenesis and leads to lipoma formation in zebrafish. *PLoS One, 7*.

Couturier, K., Batandier, C., Awada, M., Hininger-Favier, I., Canini, F., Anderson, R. A., et al. (2010). Cinnamon improves insulin sensitivity and alters the body composition in an animal model of the metabolic syndrome. *Arch Biochem Biophys, 501*(1), 158-161.

Craig Freudenrich, P. D. (2001). How Diabetes Works [Electronic Version], from https://health.howstuffworks.com/diseases-conditions/diabetes/diabetes.htm

Crowe, D. L., and Chandraratna, R. A. (2004). A retinoid X receptor (RXR)-selective retinoid reveals that RXR-alpha is potentially a therapeutic target in breast cancer cell lines, and that it potentiates antiproliferative and apoptotic responses to peroxisome proliferator-activated receptor ligands. *Breast Cancer Res, 6*(5), R546-555.

Cuzzocrea, S., Pisano, B., Dugo, L., Ianaro, A., Maffia, P., Patel, N. S., et al. (2004). Rosiglitazone, a ligand of the peroxisome proliferator-activated receptor-gamma, reduces acute inflammation. *Eur J Pharmacol, 483*(1), 79-93.

Danforth, E. (2000). Failure of adipocyte differentiation causes type II diabetes mellitus? *Nat Genet, 26*(1), 13-13.

Dawson, M. I., and Xia, Z. (2012). The Retinoid X Receptors and Their Ligands. *Biochimica et biophysica acta, 1821*(1), 21-56.

Embong, W. H. W. (2007). *Healing Herbs of Malaysia.* : Wisma Felda. Federal Land Development Authority (FELDA).

Esatbeyoglu, T., Ulbrich, K., Rehberg, C., Rohn, S., and Rimbach, G. (2015). Thermal stability, antioxidant, and anti-inflammatory activity of curcumin and its degradation product 4-vinyl guaiacol. *Food Funct, 6*(3), 887-893.

Ezure, T., and Amano, S. (2011). Rubus suavissimus S. Lee extract increases early adipogenesis in 3T3-L1 preadipocytes. *Journal of Natural Medicines, 65*(2), 247-253.

Fabbrini, E., Sullivan, S., and Klein, S. (2010). Obesity and nonalcoholic fatty liver disease: biochemical, metabolic, and clinical implications. *Hepatology, 51*(2), 679-689.

Farese, R. V., Sajan, M. P., and Standaert, M. L. (2005). Insulin-sensitive protein kinases (atypical protein kinase C and protein kinase B/Akt): actions and

defects in obesity and type II diabetes. *Exp Biol Med (Maywood), 230*(9), 593-605.

Farmer, S. (2005). Regulation of PPARgamma activity during adipogenesis. *Int J Obes (Lond), 29*(Suppl 1), S13 - 16.

Ferris, H. A., and Kahn, C. R. (2012). New mechanisms of glucocorticoid-induced insulin resistance: make no bones about it. *The Journal of Clinical Investigation, 122*(11), 3854-3857.

Fleming, A., Jankowski, J., and Goldsmith, P. (2010). In vivo analysis of gut function and disease changes in a zebrafish larvae model of inflammatory bowel disease: a feasibility study. *Inflamm Bowel Dis, 16*.

Fotakis, G., and Timbrell, J. A. (2006). In vitro cytotoxicity assays: Comparison of LDH, neutral red, MTT and protein assay in hepatoma cell lines following exposure to cadmium chloride. *Toxicology Letters, 160*(2), 171-177.

Freshney, R. I. (2010). Cytotoxicity. In *Culture of Animal Cells* (pp. 365-381): John Wiley & Sons, Inc.

Frohnert, B. I., Jacobs, D. R., Steinberger, J., Moran, A., Steffen, L. M., and Sinaiko, A. R. (2013). Relation Between Serum Free Fatty Acids and Adiposity, Insulin Resistance, and Cardiovascular Risk Factors From Adolescence to Adulthood. *Diabetes, 62*(9), 3163-3169.

Fröjdö, S., Vidal, H., and Pirola, L. (2009). Alterations of insulin signaling in type 2 diabetes: A review of the current evidence from humans. *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease, 1792*(2), 83-92.

Fu, Z., Gilbert, E. R., and Liu, D. (2013). Regulation of Insulin Synthesis and Secretion and Pancreatic Beta-Cell Dysfunction in Diabetes. *Current diabetes reviews, 9*(1), 25-53.

Fujiwara, H., Hosokawa, M., Zhou, X., Fujimoto, S., Fukuda, K., Toyoda, K., et al. (2008). Curcumin inhibits glucose production in isolated mice hepatocytes. *Diabetes Res Clin Pract, 80*(2), 185-191.

Gallo, M., Ferracane, R., Graziani, G., Ritieni, A., and Fogliano, V. (2010). Microwave assisted extraction of phenolic compounds from four different spices. *Molecules, 15*(9), 6365-6374.

Gao, Y., Yang, M. F., Su, Y. P., Jiang, H. M., You, X. J., Yang, Y. J., et al. (2013). Ginsenoside Re reduces insulin resistance through activation of PPAR-

gamma pathway and inhibition of TNF-alpha production. *J Ethnopharmacol, 147*(2), 509-516.

Garg, V., Dhar, V. J., Sharma, A., and Dutt, R. (2012). Facts about standardization of herbal medicine: a review. *Zhong Xi Yi Jie He Xue Bao, 10*(10), 1077-1083.

Ghosh, C., Yang, S. H., Kim, J. G., Jeon, T.-I., Yoon, B. H., Lee, J. Y., et al. (2013). Zinc-chelated Vitamin C Stimulates Adipogenesis of 3T3-L1 Cells. *Asian-Australas J Anim Sci, 26*(8), 1189-1196.

Gnanavel, V., and Saral, A. M. (2013). GC-MS Analysis of Petroleum Ether and Ethanol Leaf Extarcts from Abrus precatorius linn. *Int J Pharm Bio Sci, 4*(3), 8.

Gomathi, D., Ravikumar, G., Kalaiselvi, M., Devaki, K., and Uma, C. (2014). Antioxidant activity and functional group analysis of Evolvulus alsinoides. *Chinese Journal of Natural Medicines, 12*(11), 827-832.

Greenberg, A. S., and Obin, M. S. (2006). Obesity and the role of adipose tissue in inflammation and metabolism. *The American Journal of Clinical Nutrition, 83*(2), 461S-465S.

Gregoire, F. M., Smas, C. M., and Sul, H. S. (1998). Understanding Adipocyte Differentiation. *Physiological Reviews, 78*(3), 783-809.

Grygiel-Górniak, B. (2014). Peroxisome proliferator-activated receptors and their ligands: nutritional and clinical implications – a review. *Nutrition Journal, 13*, 17-17.

Gulati, V., Gulati, P., Harding, I. H., and Palombo, E. A. (2015). Exploring the anti-diabetic potential of Australian Aboriginal and Indian Ayurvedic plant extracts using cell-based assays. *BMC Complement Altern Med, 15*, 8.

Guo, S. (2014). Insulin signaling, resistance, and metabolic syndrome: insights from mouse models into disease mechanisms. *Journal of Endocrinology, 220*(2), T1-T23.

Guo, X., Zhou, G., Guo, M., Cheung, A. K., Huang, Y., and Beddhu, S. (2014). Adiponectin retards the progression of diabetic nephropathy in db/db mice by counteracting angiotensin II. *Physiological Reports, 2*(2), e00230.

Gustafson, B., Hedjazifar, S., Gogg, S., Hammarstedt, A., and Smith, U. (2015). Insulin resistance and impaired adipogenesis. *Trends Endocrinol Metab, 26*(4), 193-200.

Hallare, A., Ruiz, P., and Cariño, J. C. E. (2014). Assessment of Jatropha curcas L. biodiesel seed cake toxicity using the zebrafish (Danio rerio) embryo toxicity (ZFET) test. *Environmental Science and Pollution Research, 21*(9), 6044-6056.

Hanum, R. F. (2017, 7 April 2017). Almost 1 in 5 M'sian adults has diabetes: Health Ministry [Electronic Version]. Retrieved 15 September 2017, from https://www.nst.com.my/news/2017/04/228106/almost-1-5-msian-adults-has-diabetes-health-ministry

Harder-Lauridsen, N. M., Krogh-Madsen, R., Holst, J. J., Plomgaard, P., Leick, L., Pedersen, B. K., et al. (2014). Effect of IL-6 on the insulin sensitivity in patients with type 2 diabetes. *Am J Physiol Endocrinol Metab, 306*(7), E769-778.

Hauner, H. (2002). The mode of action of thiazolidinediones. *Diabetes Metab Res Rev, 18 Suppl 2*, S10-15.

Hausman, G. J., Poulos, S. P., Pringle, T. D., and Azain, M. J. (2008). The influence of thiazolidinediones on adipogenesis in vitro and in vivo: potential modifiers of intramuscular adipose tissue deposition in meat animals. *J Anim Sci, 86*(14 Suppl), E236-243.

Hay, N. (2011). Akt isoforms and glucose homeostasis - the leptin connection. *Trends in endocrinology and metabolism: TEM, 22*(2), 66-73.

He, Y., Li, Y., Zhao, T., Wang, Y., and Sun, C. (2013). Ursolic Acid Inhibits Adipogenesis in 3T3-L1 Adipocytes through LKB1/AMPK Pathway. *PLoS ONE, 8*(7), e70135.

Heinonen, S., Saarinen, L., Naukkarinen, J., Rodriguez, A., Fruhbeck, G., Hakkarainen, A., et al. (2014). Adipocyte morphology and implications for metabolic derangements in acquired obesity. *Int J Obes (Lond), 38*(11), 1423-1431.

Hernandez, R., Teruel, T., and Lorenzo, M. (2003). Rosiglitazone produces insulin sensitisation by increasing expression of the insulin receptor and its tyrosine kinase activity in brown adipocytes. *Diabetologia, 46*(12), 1618-1628.

Huang, C. C., Huang, W. C., Hou, C. W., Chi, Y. W., and Huang, H. Y. (2014). Effect of black soybean koji extract on glucose utilization and adipocyte differentiation in 3T3-L1 cells. *Int J Mol Sci, 15*(5), 8280-8292.

Hussein, H. M., Hameed, I. H., and Ibraheem, O. A. (2016). Antimicrobial Activity and Spectral Chemical Analysis of Methanolic Leaves Extract of Adiantum Capillus-Veneris Using GC-MS and FTIR Spectroscopy. *International Journal of Pharmacognosy and Phytochemical Research, 8*(3), 17.

Ismail, H. F., Majid, F. A. A., and Hashim, Z. (2017). Eugenia Polyantha Enhances Adipogenesis via CEBP-A and Adiponectin Overexpression in 3T3-L1. *CHEMICAL ENGINEERING TRANSACTIONS, 58*, 1117-1122.

Issemann, I., Prince, R. A., Tugwood, J. D., and Green, S. (1993). The peroxisome proliferator-activated receptor:retinoid X receptor heterodimer is activated by fatty acids and fibrate hypolipidaemic drugs. *J Mol Endocrinol, 11*(1), 37-47.

Jaganathan, S. K., and Supriyanto, E. (2012). Antiproliferative and Molecular Mechanism of Eugenol-Induced Apoptosis in Cancer Cells. *Molecules, 17*(6), 6290.

Järup, L. (2003). Hazards of heavy metal contamination. *British Medical Bulletin, 68*(1), 167-182.

Jarvill-Taylor, K. J., Anderson, R. A., and Graves, D. J. (2001). A hydroxychalcone derived from cinnamon functions as a mimetic for insulin in 3T3-L1 adipocytes. *J Am Coll Nutr, 20*(4), 327-336.

Jerah, R. E. A. L., Lihan, S., and Ahmad, I. b. (2013). The Effect Of Combination Of Octadecanoic Acid, Methyl Ester And Ribavirin Against Measles Virus. *International Journal of Scientific & Technology Research 2*(10), 4.

Jiang, G., Dallas-Yang, Q., Biswas, S., Li, Z., and Zhang, B. B. (2004). Rosiglitazone, an agonist of peroxisome-proliferator-activated receptor gamma (PPARgamma), decreases inhibitory serine phosphorylation of IRS1 in vitro and in vivo. *Biochemical Journal, 377*(Pt 2), 339-346.

Jollow, D. J., Mitchell, J. R., Zampaglione, N., and Gillete, J. R. (1974). Bromobenzene induced liver necrosis. Protective role of glutathione and evidence for 3, 4- bromobenzene oxide as a hepatotoxic metabolite. *Pharmacology, 1*.

Joshi, C. S., Priya, E. S., and Venkataraman, S. (2007). Hypoglycemic and antilipidperoxidation of polyherbal formulation Diakyur in experimentally induced diabetes. J. *Journal of Health Science, 53*(6), 6.

Joshi, D. D. (2012). FTIR Spectroscopy: Herbal Drugs and Fingerprints. In *Herbal Drugs and Fingerprints: Evidence Based Herbal Drugs* (pp. 121-146). India: Springer India.

Kalra, S., Aamir, A. H., Raza, A., Das, A. K., Azad Khan, A. K., Shrestha, D., et al. (2015). Place of sulfonylureas in the management of type 2 diabetes mellitus in South Asia: A consensus statement. *Indian Journal of Endocrinology and Metabolism, 19*(5), 577-596.

Kalueff, A. V., Stewart, A. M., and Gerlai, R. (2014). Zebrafish as an emerging model for studying complex brain disorders. *Trends Pharmacol Sci, 35*.

Kang, S.-I., Shin, H.-S., and Kim, S.-J. (2015). Sinensetin Enhances Adipogenesis and Lipolysis by Increasing Cyclic Adenosine Monophosphate Levels in 3T3-L1 Adipocytes. *Biological and Pharmaceutical Bulletin, 38*(4), 552-558.

Kannan, R. R., and Vincent, S. G. P. (2012). Cynodon dactylon and Sida acuta extracts impact on the function of the cardiovascular system in zebrafish embryos. *Journal of Biomedical Research, 26*(2), 90-97.

Kanoh, Y., Bandyopadhyay, G., Sajan, M. P., Standaert, M. L., and Farese, R. V. (2001). Rosiglitazone, insulin treatment, and fasting correct defective activation of protein kinase C-zeta/lambda by insulin in vastus lateralis muscles and adipocytes of diabetic rats. *Endocrinology, 142*(4), 1595-1605.

Kanungo, J., Cuevas, E., Ali, S. F., and Paule, M. G. (2014). Zebrafish Model in Drug Safety Assessment. *Curr Pharm Des, 20*.

Katiyar, D., Singh, V., Gilani, S. J., Goel, R., Grover, P., and Vats, A. (2015). Hypoglycemic herbs and their polyherbal formulations: a comprehensive review. *Medicinal Chemistry Research, 24*(1), 1-21.

Kato, E., Nakagomi, R., Gunawan-Puteri, M. D., and Kawabata, J. (2013). Identification of hydroxychavicol and its dimers, the lipase inhibitors contained in the Indonesian spice, Eugenia polyantha. *Food Chem, 136*(3-4), 1239-1242.

Khuwijitjaru, P., Sayputikasikorn, N., Samuhasaneetoo, S., Penroj, P., Siriwongwilaichat, P., and Adachi, S. (2012). Subcritical water extraction of flavoring and phenolic compounds from cinnamon bark (Cinnamomum zeylanicum). *J Oleo Sci, 61*(6), 349-355.

Kido, Y., Nakae, J., and Accili, D. (2001). The Insulin Receptor and Its Cellular Targets. *The Journal of Clinical Endocrinology & Metabolism, 86*(3), 972-979.

Kim, B., Choi, K. M., Yim, H. S., and Lee, M.-G. (2013). Ascorbic acid enhances adipogenesis of 3T3-L1 murine preadipocyte through differential expression of collagens. *Lipids in Health and Disease, 12*, 182-182.

Kim, G.-S., Park, H. J., Woo, J.-H., Kim, M.-K., Koh, P.-O., Min, W., et al. (2012). Citrus aurantium flavonoids inhibit adipogenesis through the Akt signaling pathway in 3T3-L1 cells. *BMC Complementary and Alternative Medicine, 12*(1), 31.

Kim, T., Davis, J., Zhang, A. J., He, X., and Mathews, S. T. (2009). Curcumin activates AMPK and suppresses gluconeogenic gene expression in hepatoma cells. *Biochem Biophys Res Commun, 388*(2), 377-382.

King, A. V., and Jones, P. A. (2003). In-house assessment of a modified in vitro cytotoxicity assay for higher throughput estimation of acute toxicity. *Toxicology in Vitro, 17*(5–6), 717-722.

Koster, J. C., Permutt, M. A., and Nichols, C. G. (2005). Diabetes and Insulin Secretion: The ATP-Sensitive K+ Channel (KATP) Connection. *Diabetes, 54*(11), 3065-3072.

Kulkarni, K. M., Patil, L. S., Khanvilkar, M. V. V., and Kadam, D. V. J. (2014). FINGERPRINTING TECHNIQUES IN HERBAL STANDARDIZATION. *IAJPR, 4*(2), 1049-1062.

Kulkarni, M. V., Kulkarni, G. M., Lin, C. H., and Sun, C. M. (2006). Recent advances in coumarins and 1-azacoumarins as versatile biodynamic agents. *Curr Med Chem, 13*(23), 2795-2818.

Kumar, R., Kerins, D. M., and Walther, T. (2016). Cardiovascular safety of anti-diabetic drugs. *European Heart Journal - Cardiovascular Pharmacotherapy, 2*(1), 32-43.

Kundu, P. K., and Chatterjee, P. (2010). Meta-analysis of Diabecon Tablets: Efficacy and Safety Outcomes from 15 Clinical Trials in Diabetes Mellitus. *Indian Journal of Clinical Practice, 20*(9), 7.

Kusminski, Christine M., Mcternan, Philip G., and Kumar, S. (2005). Role of resistin in obesity, insulin resistance and Type II diabetes. *Clinical Science, 109*(3), 243-256.

Lanjhiyana, S., Garabadu, D., Ahirwar, D., Rana, A. C., Ahirwar, B., and Lanjhiyana, S. K. (2011). Pharmacognostic Standardization and Hypoglycemic Evaluations of Novel Polyherbal Formulations *Der Pharmacia Lettre, 3*(1), 15.

Lebovitz, H. E., and Banerji, M. A. (2001). Insulin resistance and its treatment by thiazolidinediones. *Recent Prog Horm Res, 56*, 265-294.

Lechtenberg, M., Quandt, B., and Nahrstedt, A. (2004). Quantitative determination of curcuminoids in Curcuma rhizomes and rapid differentiation of Curcuma domestica Val. and Curcuma xanthorrhiza Roxb. by capillary electrophoresis. *Phytochem Anal, 15*(3), 152-158.

Lee, M.-J., Pramyothin, P., Karastergiou, K., and Fried, S. K. (2014). Deconstructing the roles of glucocorticoids in adipose tissue biology and the development of central obesity. *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease, 1842*(3), 473-481.

Lee, Y. J., Choi, H. S., Seo, M. J., Jeon, H. J., Kim, K. J., and Lee, B. Y. (2015). Kaempferol suppresses lipid accumulation by inhibiting early adipogenesis in 3T3-L1 cells and zebrafish. *Food Funct, 6*(8), 2824-2833.

Lehmann, J. M., Moore, L. B., Smith-Oliver, T. A., Wilkison, W. O., Willson, T. M., and Kliewer, S. A. (1995). An antidiabetic thiazolidinedione is a high affinity ligand for peroxisome proliferator-activated receptor gamma (PPAR gamma). *J Biol Chem, 270*(22), 12953-12956.

Lelono, R. A., and Tachibana, S. (2013). Bioassay-guided isolation and identification of antioxidative compounds from the bark of Eugenia polyantha. *Pak J Biol Sci, 16*(16), 812-818.

Lelono, R. A., Tachibana, S., and Itoh, K. (2009). In vitro antioxidative activities and polyphenol content of Eugenia polyantha Wight grown in Indonesia. *Pak J Biol Sci, 12*(24), 1564-1570.

Liang, X.-m., Jin, Y., Feng, J.-t., and Ke, Y.-x. (2011). Identification and Structure Elucidation of Compounds from Herbal Medicines. In *Traditional Herbal Medicine Research Methods* (pp. 139-223): John Wiley & Sons, Inc.

Liang, Y.-Z., Xie, P., and Chan, K. (2004). Quality control of herbal medicines. *Journal of Chromatography B, 812*(1–2), 53-70.

Lin, H. V., Kim, J. Y., Pocai, A., Rossetti, L., Shapiro, L., Scherer, P. E., et al. (2007). Adiponectin resistance exacerbates insulin resistance in insulin receptor transgenic/knockout mice. *Diabetes, 56*(8), 1969-1976.

Lin, J., and Chen, A. (2011). Curcumin diminishes the impacts of hyperglycemia on the activation of hepatic stellate cells by suppressing membrane translocation and gene expression of glucose transporter-2. *Mol Cell Endocrinol, 333*(2), 160-171.

Liu, Q., Kim, S. B., Ahn, J. H., Hwang, B. Y., Kim, S. Y., and Lee, M. K. (2012). Anthraquinones from Morinda officinalis roots enhance adipocyte differentiation in 3T3-L1 cells. *Natural Product Research, 26*(18), 1750-1754.

Liu, Y., Kretz, C. A., Maeder, M. L., Richter, C. E., Tsao, P., Vo, A. H., et al. (2014). Targeted mutagenesis of zebrafish antithrombin III triggers disseminated intravascular coagulation and thrombosis, revealing insight into function. *Blood, 124*(1), 142-150.

Lonn, M., Mehlig, K., Bengtsson, C., and Lissner, L. (2010). Adipocyte size predicts incidence of type 2 diabetes in women. *FASEB J, 24*(1), 326-331.

Lowe, C. E., O'Rahilly, S., and Rochford, J. J. (2011). Adipogenesis at a glance. *Journal of Cell Science, 124*(16), 2681-2686.

Lowell, B. B. (1999). An Essential Regulator of Adipogenesis and Modulator of Fat Cell Function: PPARγ. *Cell, 99*(3), 239-242.

Maeda, N., Takahashi, M., Funahashi, T., Kihara, S., Nishizawa, H., Kishida, K., et al. (2001). PPARgamma ligands increase expression and plasma concentrations of adiponectin, an adipose-derived protein. *Diabetes, 50*(9), 2094-2099.

Mandlik, R. V., Desai, S. K., Naik, S. R., Sharma, G., and Kohli, R. K. (2008). Antidiabetic activity of a polyherbal formulation (DRF/AY/5001). *Indian J Exp Biol, 46*(8), 599-606.

Mandrell, D., Truong, L., Jephson, C., Sarker, M. R., Moore, A., Lang, C., et al. (2012). Automated Zebrafish Chorion Removal and Single Embryo Placement: Optimizing Throughput of Zebrafish Developmental Toxicity Screens. *Journal of Laboratory Automation, 17*(1), 66-74.

Mandrup, S., and Lane, M. D. (1997). Regulating adipogenesis. *J Biol Chem, 2*.

Mateos-Martin, M. L., Fuguet, E., Quero, C., Perez-Jimenez, J., and Torres, J. L. (2012). New identification of proanthocyanidins in cinnamon (Cinnamomum zeylanicum L.) using MALDI-TOF/TOF mass spectrometry. *Anal Bioanal Chem, 402*(3), 1327-1336.

Mazor, R., Alsaigh, T., and Schmid-Schonbein, G. (2012). Increased protease activity in obese rats: implications on LDL and insulin receptors. *The FASEB Journal, 26*(1 Supplement), 567.563.

McHugh, M. (2006). Fit or fat? A review of the debate on deaths attributable to obesity. *Public Health Nurs, 23*(3), 264 - 270.

Medina-Gomez, G., Gray, S., and Vidal-Puig, A. (2007). Adipogenesis and lipotoxicity: role of peroxisome proliferator-activated receptor gamma (PPARgamma) and PPARgammacoactivator-1 (PGC1). *Public Health Nutr, 10*(10A), 1132-1137.

Meshkani, R., Sadeghi, A., Taheripak, G., Zarghooni, M., Gerayesh-Nejad, S., and Bakhtiyari, S. (2014). Rosiglitazone, a PPARgamma agonist, ameliorates palmitate-induced insulin resistance and apoptosis in skeletal muscle cells. *Cell Biochem Funct, 32*(8), 683-691.

Modak, M., Dixit, P., Londhe, J., Ghaskadbi, S., and Paul A. Devasagayam, T. (2007). Indian Herbs and Herbal Drugs Used for the Treatment of Diabetes. *Journal of Clinical Biochemistry and Nutrition, 40*(3), 163-173.

Moghadam-Kia, S., and Werth, V. P. (2010). Prevention and treatment of systemic glucocorticoid side effects. *International journal of dermatology, 49*(3), 239-248.

Mohamed, E. A. H., Siddiqui, M. J. A., Ang, L. F., Sadikun, A., Chan, S. H., Tan, S. C., et al. (2012). Potent α-glucosidase and α-amylase inhibitory activities of standardized 50% ethanolic extracts and sinensetin from Orthosiphon stamineus Benth as anti-diabetic mechanism. *BMC Complementary and Alternative Medicine, 12*(1), 1-7.

Moller, D. (2001). New drug targets for type 2 diabetes and the metabolic syndrome. *Nature, 414*(6865), 821 - 827.

Moseti, D., Regassa, A., and Kim, W. K. (2016). Molecular Regulation of Adipogenesis and Potential Anti-Adipogenic Bioactive Molecules. *Int J Mol Sci, 17*(1).

Muller, E. B., Lin, S., and Nisbet, R. M. (2015). Quantitative Adverse Outcome Pathway Analysis of Hatching in Zebrafish with CuO Nanoparticles. *Environmental Science & Technology, 49*(19), 11817-11824.

Müller, G. (2011). Let's shift lipid burden—From large to small adipocytes. *European Journal of Pharmacology, 656*(1–3), 1-4.

Musa, M. A., Cooperwood, J. S., and Khan, M. O. (2008). A review of coumarin derivatives in pharmacotherapy of breast cancer. *Curr Med Chem, 15*(26), 2664-2679.

Nahas, R., and Moher, M. (2009). Complementary and alternative medicine for the treatment of type 2 diabetes. *Can Fam Physician, 55*(6), 591-596.

Nakamura, K., Fuster, J. J., and Walsh, K. (2014). Adipokines: A link between obesity and cardiovascular disease. *Journal of Cardiology, 63*(4), 250-259.

Nathan, D. M., Buse, J. B., Davidson, M. B., Heine, R. J., Holman, R. R., Sherwin, R., et al. (2006). Management of Hyperglycemia in Type 2 Diabetes: A Consensus Algorithm for the Initiation and Adjustment of Therapy. *Diabetes Care, 29*(8), 1963.

Niethammer, P., Grabher, C., Look, A. T., and Mitchison, T. J. (2009). A tissue-scale gradient of hydrogen peroxide mediates rapid wound detection in zebrafish. *Nature, 459*.

Nigro, E., Scudiero, O., Monaco, M. L., Palmieri, A., Mazzarella, G., Costagliola, C., et al. (2014). New Insight into Adiponectin Role in Obesity and Obesity-Related Diseases. *BioMed Research International, 2014*, 14.

Nipanikar, S. U., Chitlange, S. S., and Nagore, D. (2017). Evaluation of anti-diabetic activity of AHPL/AYTAB/0513 tablet in streptozotocin induced diabetes in rats. *International Journal of Pharmaceutical Investigation, 7*(1), 25-32.

NPRA. (2017). *Cancellation of Notified Cosmetic Products*. Petaling Jaya, Selangor: National Pharmaceutical Ragulatory Agency o. Document Number)

Ntambi, J., and Young-Cheul, K. (2000). Adipocyte differentiation and gene expression. *J Nutr, 130*(12), 3122S - 3126S.

O'Brien, K., Sekimoto, H., Boney, C., and Malee, M. (2008). Effect of fetal dexamethasone exposure on the development of adult insulin sensitivity in a rat model. *J Matern Fetal Neonatal Med, 21*(9), 623-628.

OECD. *Test No. 236: Fish Embryo Acute Toxicity (FET) Test*: OECD Publishing.

Ong, E. S. (2004). Extraction methods and chemical standardization of botanicals and herbal preparations. *Journal of Chromatography B, 812*(1–2), 23-33.

Oon, S. F., Nallappan, M., Tee, T. T., Shohaimi, S., Kassim, N. K., Sa'ariwijaya, M. S. F., et al. (2015). Xanthorrhizol: a review of its pharmacological activities and anticancer properties. *Cancer Cell International, 15*(1), 1-15.

Pandey, M. R., and Guo, H. (2014). Evaluation of cytotoxicity, genotoxicity and embryotoxicity of insecticide propoxur using flounder gill (FG) cells and zebrafish embryos. *Toxicology in Vitro, 28*(3), 340-353.

Pari, L., and Saravanan, R. (2004). Antidiabetic effect of diasulin, a herbal drug, on blood glucose, plasma insulin and hepatic enzymes of glucose metabolism in hyperglycaemic rats. *Diabetes Obes Metab, 6*(4), 286-292.

Parsons, M. J., Campos, I., Hirst, E. M., and Stemple, D. L. (2002). Removal of dystroglycan causes severe muscular dystrophy in zebrafish embryos. *Development, 129*.

Pasarica, M., Xie, H., Hymel, D., Bray, G., Greenway, F., Ravussin, E., et al. (2009). Lower total adipocyte number but no evidence for small adipocyte depletion in patients with type 2 diabetes. *Diabetes Care, 32*(5), 900-902.

Patel, S. S., Shah, R. S., and Goyal, R. K. (2009). Antihyperglycemic, antihyperlipidemic and antioxidant effects of Dihar, a polyherbal ayurvedic formulation in streptozotocin induced diabetic rats. *Indian J Exp Biol, 47*(7), 564-570.

Penumetcha, M., and Santanam, N. (2012). Nutraceuticals as Ligands of PPAR. *PPAR Research, 2012*, 7.

Pessin, J. E., and Saltiel, A. R. (2000). Signaling pathways in insulin action: molecular targets of insulin resistance. *Journal of Clinical Investigation, 106*(2), 165-169.

Prabhakar, P. K., and Doble, M. (2011). Effect of Natural Products on Commercial Oral Antidiabetic Drugs in Enhancing 2-Deoxyglucose Uptake by 3T3-L1 Adipocytes. *Ther Adv Endocrinol Metab, 2*(3), 103-114.

Prasad, R. C., Herzog, B., Boone, B., Sims, L., and Waltner-Law, M. (2005). An extract of Syzygium aromaticum represses genes encoding hepatic gluconeogenic enzymes. *J Ethnopharmacol, 96*(1-2), 295-301.

Qader, S. W., Abdulla, M. A., Chua, L. S., Najim, N., Zain, M. M., and Hamdan, S. (2011). Antioxidant, total phenolic content and cytotoxicity evaluation of selected Malaysian plants. *Molecules, 16*(4), 3433-3443.

Qadri, N. M., Zakir-ur-Rehman, and K., S. (2006). Evaluation of Antidiabetic Activity of Dibarid, A Herbal Formulation in Type-II Diabetic Patients. *Journal of Chemical Social Pakistan, 28*(3), 3.

Qadri, N. M., Zakir-ur-Rehman, and Rizvi, H. A. (2011). Evaluation of Herbal Drug for Hypoglycemic Activity in Normal, Hyperglycemic and Alloxan-Induced Diabetic Rabbits. *Pakistan Journal of Chemistry, 1*(1), 6.

Qi, D., Pulinilkunnil, T., An, D., Ghosh, S., Abrahani, A., Pospisilik, J. A., et al. (2004). Single-Dose Dexamethasone Induces Whole-Body Insulin Resistance and Alters Both Cardiac Fatty Acid and Carbohydrate Metabolism. *Diabetes, 53*(7), 1790-1797.

Qin, B., Nagasaki, M., Ren, M., Bajotto, G., Oshida, Y., and Sato, Y. (2003). Cinnamon extract (traditional herb) potentiates in vivo insulin-regulated glucose utilization via enhancing insulin signaling in rats. *Diabetes Res Clin Pract, 62*(3), 139-148.

Qin, B., Panickar, K. S., and Anderson, R. A. (2010). Cinnamon: potential role in the prevention of insulin resistance, metabolic syndrome, and type 2 diabetes. *J Diabetes Sci Technol, 4*(3), 685-693.

Qin, J.-H., Ma, J.-Z., Yang, X.-W., Hu, Y.-J., Zhou, J., Fu, L.-C., et al. (2015). A Triterpenoid Inhibited Hormone-Induced Adipocyte Differentiation and Alleviated Dexamethasone-Induced Insulin Resistance in 3T3-L1 adipocytes. *Natural Products and Bioprospecting, 5*(3), 159-166.

Rafehi, H., Ververis, K., and Karagiannis, T. C. (2012). Controversies surrounding the clinical potential of cinnamon for the management of diabetes. *Diabetes Obes Metab, 14*(6), 493-499.

Rajala, M. W., Qi, Y., Patel, H. R., Takahashi, N., Banerjee, R., Pajvani, U. B., et al. (2004). Regulation of resistin expression and circulating levels in obesity, diabetes, and fasting. *Diabetes, 53*(7), 1671-1679.

Ramji, D. P., and Foka, P. (2002). CCAAT/enhancer-binding proteins: structure, function and regulation. *Biochemical Journal, 365*(Pt 3), 561-575.

Rao, P. R., and Rathod, V. K. (2015). Rapid extraction of andrographolide from Andrographis paniculata Nees by three phase partitioning and determination

of its antioxidant activity. *Biocatalysis and Agricultural Biotechnology, 4*(4), 586-593.

Rao, P. V., and Gan, S. H. (2014). Cinnamon: A Multifaceted Medicinal Plant. *Evidence-Based Complementary and Alternative Medicine, 2014*, 12.

Reichert, M., and Eick, D. (1999). Analysis of cell cycle arrest in adipocyte differentiation. *Oncogene, 18*(2), 459-466.

Ren, D., Collingwood, T. N., Rebar, E. J., Wolffe, A. P., and Camp, H. S. (2002). PPARγ knockdown by engineered transcription factors: exogenous PPARγ2 but not PPARγ1 reactivates adipogenesis. *Genes & Development, 16*(1), 27-32.

Rhee, M. S., Perianayagam, A., Chen, P., Youn, J. H., and McDonough, A. A. (2004). Dexamethasone treatment causes resistance to insulin-stimulated cellular potassium uptake in the rat. *American Journal of Physiology - Cell Physiology, 287*(5), C1229-C1237.

Rizzo, L. Y., Golombek, S. K., Mertens, M. E., Pan, Y., Laaf, D., Broda, J., et al. (2013). In Vivo Nanotoxicity Testing using the Zebrafish Embryo Assay. *Journal of materials chemistry. B, Materials for biology and medicine, 1*, 10.1039/C1033TB20528B.

Roden, M. (2004). How Free Fatty Acids Inhibit Glucose Utilization in Human Skeletal Muscle. *Physiology, 19*(3), 92-96.

Rodriguez, A., Ezquerro, S., Mendez-Gimenez, L., Becerril, S., and Fruhbeck, G. (2015). Revisiting the adipocyte: a model for integration of cytokine signaling in the regulation of energy metabolism. *Am J Physiol Endocrinol Metab, 309*(8), E691-714.

Rosen, E., Walkey, C., Puigserver, P., and Spiegelman, B. (2000). Transcriptional regulation of adipogenesis. *Genes Dev, 14*(11), 1293 - 1307.

Rosen, E. D., Hsu, C.-H., Wang, X., Sakai, S., Freeman, M. W., Gonzalez, F. J., et al. (2002). C/EBPα induces adipogenesis through PPARγ: a unified pathway. *Genes & Development, 16*(1), 22-26.

Saad, M. J., Folli, F., Kahn, J. A., and Kahn, C. R. (1993). Modulation of insulin receptor, insulin receptor substrate-1, and phosphatidylinositol 3-kinase in liver and muscle of dexamethasone-treated rats. *Journal of Clinical Investigation, 92*(4), 2065-2072.

Saidan, N., Aisha, A., Mohd Hamil, S., Abdul Malik, A., and Ismail, Z. (2015a). A novel reverse phase high performance liquid chromatography method for standardization of Orthosiphon stamineus leaf extracts. *Pharmacognosy Res, 7*.

Saidan, N. H., Hamil, M. S. R., Memon, A. H., Abdelbari, M. M., Hamdan, M. R., Mohd, K. S., et al. (2015b). Selected metabolites profiling of Orthosiphon stamineus Benth leaves extracts combined with chemometrics analysis and correlation with biological activities. *BMC Complementary and Alternative Medicine, 15*, 350.

Saifudin, A., Tanaka, K., Kadota, S., and Tezuka, Y. (2012). Protein tyrosine phosphatase 1B (PTP1B)-inhibiting constituents from the leaves of Syzygium polyanthum. *Planta Med, 78*(12), 1378-1381.

Saini, V. (2010). Molecular mechanisms of insulin resistance in type 2 diabetes mellitus. *World Journal of Diabetes, 1*(3), 68-75.

Saito, T., Abe, D., and Sekiya, K. (2008). Sakuranetin induces adipogenesis of 3T3-L1 cells through enhanced expression of PPARγ2. *Biochemical and Biophysical Research Communications, 372*(4), 835-839.

Sajeeth C.I, Manna P.K , R. Manavalan2 , and C.I, J. (2010). Phytochemical Investigation and Antioxidant Activity of a Polyherbal Formulation (ESF/AY/500) on Streptozotocin Induced Oxidative Stress in Rats *Der Pharma Chemica, 2*(5), 6.

Sakoda, H., Ogihara, T., Anai, M., Funaki, M., Inukai, K., Katagiri, H., et al. (2000). Dexamethasone-induced insulin resistance in 3T3-L1 adipocytes is due to inhibition of glucose transport rather than insulin signal transduction. *Diabetes, 49*(10), 1700-1708.

Salans, L. B., Knittle, J. L., and Hirsch, J. (1968). The role of adipose cell size and adipose tissue insulin sensitivity in the carbohydrate intolerance of human obesity. *J Clin Invest, 47*(1), 153-165.

Samson, J. C., Goodridge, R., Olobatuyi, F., and Weis, J. S. (2001). Delayed effects of embryonic exposure of zebrafish (Danio rerio) to methylmercury (MeHg). *Aquatic Toxicology, 51*(4), 369-376.

Sangeetha, K. N., Shilpa, K., Jyothi Kumari, P., and Lakshmi, B. S. (2013). Reversal of dexamethasone induced insulin resistance in 3T3L1 adipocytes by 3beta-taraxerol of Mangifera indica. *Phytomedicine, 20*(3-4), 213-220.

Schäcke, H., Döcke, W.-D., and Asadullah, K. (2002). Mechanisms involved in the side effects of glucocorticoids. *Pharmacology & Therapeutics, 96*(1), 23-43.

Schaffler, A., Scholmerich, J., and Salzberger, B. (2007). Adipose tissue as an immunological organ: Toll-like receptors, C1q/TNFs and CTRPs. *Trends Immunol, 28*(9), 393 - 399.

Schrage, A., Hempel, K., Schulz, M., Kolle, S. N., Van Ravenzwaay, B., and Landsiedel, R. (2011). Refinement and reduction of acute oral toxicity testing: A critical review of the use of cytotoxicity data. *ATLA Alternatives to Laboratory Animals, 39*(3), 273-295.

Seino, S., Shibasaki, T., and Minami, K. (2011). Dynamics of insulin secretion and the clinical implications for obesity and diabetes. *The Journal of Clinical Investigation, 121*(6), 2118-2125.

Shang, W., Yang, Y., Jiang, B., Jin, H., Zhou, L., Liu, S., et al. (2007). Ginsenoside Rb1 promotes adipogenesis in 3T3-L1 cells by enhancing PPARγ2 and C/EBPα gene expression. *Life Sciences, 80*(7), 618-625.

Sharabi, Y., Oron-Herman, M., Kamari, Y., Avni, I., Peleg, E., Shabtay, Z., et al. (2007). Effect of PPAR-gamma agonist on adiponectin levels in the metabolic syndrome: lessons from the high fructose fed rat model. *Am J Hypertens, 20*(2), 206-210.

Shen, Y., Fukushima, M., Ito, Y., Muraki, E., Hosono, T., Seki, T., et al. (2010). Verification of the antidiabetic effects of cinnamon (Cinnamomum zeylanicum) using insulin-uncontrolled type 1 diabetic rats and cultured adipocytes. *Biosci Biotechnol Biochem, 74*(12), 2418-2425.

Shi, J., and Kandror, K. V. (2008). Study of glucose uptake in adipose cells. *Methods Mol Biol, 456*, 307-315.

Singh, S. K., Jha, S. K., Chaudhary, A., Yadava, R. D. S., and Rai, S. B. (2010). Quality control of herbal medicines by using spectroscopic techniques and multivariate statistical analysis. *Pharmaceutical Biology, 48*(2), 134-141.

Singla, P., Bardoloi, A., and Parkash, A. A. (2010). Metabolic effects of obesity: A review. *World J Diabetes, 1*(3), 76-88.

Soni, H., Patel, S., Patel, G., and Paranjape, A. (2014). Evaluation of anti-diabetic activity of Glucova Active Tablet on Type I and Type II diabetic model in rats. *Journal of Ayurveda and Integrative Medicine, 5*(2), 97-103.

Srinivasan, K. (2014). Antioxidant potential of spices and their active constituents. *Crit Rev Food Sci Nutr, 54*(3), 352-372.

Sriplang, K., Adisakwattana, S., Rungsipipat, A., and Yibchok-Anun, S. (2007). Effects of Orthosiphon stamineus aqueous extract on plasma glucose concentration and lipid profile in normal and streptozotocin-induced diabetic rats. *J Ethnopharmacol, 109*(3), 510-514.

Studiawan, H., and Santosa, M., H. (2005). Uji Aktivitas Penurun Kadar Glukosa Darah Ekstrak Daun Eugenia polyantha pada Mencit yang Diinduksi Aloksan. *Media Kedokteran Hewan, 21*(5), 5.

Subash-Babu, P., Alshatwi, A. A., and Ignacimuthu, S. (2014). Beneficial Antioxidative and Antiperoxidative Effect of Cinnamaldehyde Protect Streptozotocin-Induced Pancreatic β-Cells Damage in Wistar Rats. *Biomolecules & Therapeutics, 22*(1), 47-54.

Sukumaran, S., DuBois, D. C., Jusko, W. J., and Almon, R. R. (2012). Glucocorticoid Effects on Adiponectin Expression. *Vitamins and hormones, 90*, 163-186.

Tang, Y., and Chen, A. (2010). Curcumin prevents leptin raising glucose levels in hepatic stellate cells by blocking translocation of glucose transporter-4 and increasing glucokinase. *Br J Pharmacol, 161*(5), 1137-1149.

Tappy, L., Randin, D., Vollenweider, P., Vollenweider, L., Paquot, N., Scherrer, U., et al. (1994). Mechanisms of dexamethasone-induced insulin resistance in healthy humans. *J Clin Endocrinol Metab, 79*(4), 1063-1069.

Tayade, P. M., Jagtap, S. A., Borde, S., Chandrasekar, N., and Joshi, A. (2012). Effect of Psoralea corylifolia on dexamethasone-induced insulin resistance in mice. *Journal of King Saud University - Science, 24*(3), 251-255.

Thakkar, N. V., and Patel, J. A. (2010). Pharmacological evaluation of "Glyoherb": A polyherbal formulation on streptozotocin-induced diabetic rats. *International Journal of Diabetes in Developing Countries, 30*(1), 1-7.

The Diabetes Prevention Program Research, G. (2012). Long-Term Safety, Tolerability, and Weight Loss Associated With Metformin in the Diabetes Prevention Program Outcomes Study. *Diabetes Care, 35*(4), 731-737.

Traver, D., Herbomel, P., Patton, E. E., Murphey, R. D., Yoder, J. A., and Litman, G. W. (2003). The zebrafish as a model organism to study development of the immune system. *Adv Immunol, 81*.

Trostler, N., Amin, R., and Shafrir, E. (1982). Increased protease activity in muscles of obese- (ob/ob) mice. *Int J Obes, 6*(6), 557-566.

Tsai, C.-Y., Peh, M. T., Feng, W., Dymock, B. W., and Moore, P. K. (2015). Hydrogen Sulfide Promotes Adipogenesis in 3T3L1 Cells. *PLOS ONE, 10*(3), e0119511.

Ukelis, U., Kramer, P.-J., Olejniczak, K., and Mueller, S. O. (2008). Replacement of in vivo acute oral toxicity studies by in vitro cytotoxicity methods: Opportunities, limits and regulatory status. *Regulatory Toxicology and Pharmacology, 51*(1), 108-118.

van Breemen, R. B., Fong, H. H., and Farnsworth, N. R. (2007). The role of quality assurance and standardization in the safety of botanical dietary supplements. *Chem Res Toxicol, 20*(4), 577-582.

Villacorta, L., Schopfer, F. J., Zhang, J., Freeman, B. A., and Chen, Y. E. (2009). PPARγ and its ligands: therapeutic implications in cardiovascular disease. *Clinical science (London, England : 1979), 116*(3), 205-218.

Vu, N., Lou, J. R., and Kupiec, T. C. (2014). Quality Control: microbial limit tests for nonsterile pharmaceuticals, part 2. *Int J Pharm Compd, 18*(4), 305-310.

Wang, F., Mullican, S. E., DiSpirito, J. R., Peed, L. C., and Lazar, M. A. (2013). Lipoatrophy and severe metabolic disturbance in mice with fat-specific deletion of PPARγ. *Proceedings of the National Academy of Sciences, 110*(46), 18656-18661.

Wang, L., Waltenberger, B., Pferschy-Wenzig, E.-M., Blunder, M., Liu, X., Malainer, C., et al. (2014). Natural product agonists of peroxisome proliferator-activated receptor gamma (PPARγ): a review. *Biochemical Pharmacology, 92*(1), 73-89.

Weinstein, S. P., Paquin, T., Pritsker, A., and Haber, R. S. (1995). Glucocorticoid-induced insulin resistance: dexamethasone inhibits the activation of glucose transport in rat skeletal muscle by both insulin- and non-insulin-related stimuli. *Diabetes, 44*(4), 441-445.

Weng, J. R., Chen, C. Y., Pinzone, J. J., Ringel, M. D., and Chen, C. S. (2006). Beyond peroxisome proliferator-activated receptor gamma signaling: the multi-facets of the antitumor effect of thiazolidinediones. *Endocr Relat Cancer, 13*.

Weyermann, J., Lochmann, D., and Zimmer, A. (2005). A practical note on the use of cytotoxicity assays. *International Journal of Pharmaceutics, 288*(2), 369-376.

WHO. (2007). WHO guidelines for assessing quality of herbal medicines with reference to contaminants and residues, *Introduction*. Geneva, Switzerland: World Health Organization

Witaicenis, A., Seito, L. N., da Silveira Chagas, A., de Almeida Junior, L. D., Luchini, A. C., Rodrigues-Orsi, P., et al. (2014). Antioxidant and intestinal anti-inflammatory effects of plant-derived coumarin derivatives. *Phytomedicine, 21*(3), 240-246.

Wolfe, R. R., Nadel, E. R., Shaw, J. H., Stephenson, L. A., and Wolfe, M. H. (1986). Role of changes in insulin and glucagon in glucose homeostasis in exercise. *Journal of Clinical Investigation, 77*(3), 900-907.

Wong, T. S., Hashim, Z., Zulkifli, R. M., Zainol, H. F. I. S. N., Rajib, N. S. M., Teh, L. C., et al. (2017). LD 50 Estimations for Diabecine TM Polyherbal Extracts Based on In Vitro Diabetic Models of 3T3-L1, WRL-68 and 1.1B4 Cell Lines. *Chemical Engineering Transactions, 56*, 6.

Wu, Z., Rosen, E., Brun, R., Hauser, S., Adelmant, G., Troy, A., et al. (1999). Cross-regulation of C/EBP alpha and PPAR gamma controls the transcriptional pathway of adipogenesis and insulin sensitivity. *Mol Cell, 3*(2), 151 - 158.

Xu, J., and Liao, K. (2004). Protein Kinase B/AKT 1 Plays a Pivotal Role in Insulin-like Growth Factor-1 Receptor Signaling Induced 3T3-L1 Adipocyte Differentiation. *Journal of Biological Chemistry, 279*(34), 35914-35922.

Xu, R., Chen, Y., Wan, D., and Wang, J. (2012). Identification of four Sedum plant medicines by fourier transform infrared spectra. *Pharmacognosy Magazine, 8*(30), 107-110.

Yang, J.-y., and Wang, L.-h. (2011). Safety Pharmacology and Toxicity Study of Herbal Medicines. In *Traditional Herbal Medicine Research Methods* (pp. 303-342): John Wiley & Sons, Inc.

Yeo, J., Kang, Y. M., Cho, S. I., and Jung, M. H. (2011). Effects of a multi-herbal extract on type 2 diabetes. *Chin Med, 6*, 10.

Yoon, Y.-S., Ryu, D., Lee, M.-W., Hong, S., and Koo, S.-H. (2009). Adiponectin and thiazolidinedione targets CRTC2 to regulate hepatic gluconeogenesis. *Experimental & Molecular Medicine, 41*(8), 577-583.

Yoshizumi, T., Ohta, T., Ninomiya, I., Terada, I., Fushida, S., Fujimura, T., et al. (2004). Thiazolidinedione, a peroxisome proliferator-activated receptor-gamma ligand, inhibits growth and metastasis of HT-29 human colon cancer cells through differentiation-promoting effects. *Int J Oncol, 25*(3), 631-639.

Yu, J. G., Javorschi, S., Hevener, A. L., Kruszynska, Y. T., Norman, R. A., Sinha, M., et al. (2002). The effect of thiazolidinediones on plasma adiponectin levels in normal, obese, and type 2 diabetic subjects. *Diabetes, 51*(10), 2968-2974.

Yuan, X., Chapman, R. L., and Wu, Z. (2011). Analytical methods for heavy metals in herbal medicines. *Phytochem Anal, 22*(3), 189-198.

Zakaria, M. H. (2015). Review of Policies and Issues in the Malaysian Herbal Industry [Electronic Version]. Retrieved 12 January 2017, from http://ap.fftc.agnet.org/ap_db.php?id=395

Zebisch, K., Voigt, V., Wabitsch, M., and Brandsch, M. (2012). Protocol for effective differentiation of 3T3-L1 cells to adipocytes. *Anal Biochem, 425*(1), 88-90.

Zeng, J.-g., Tan, M.-l., Peng, X., and Luo, Q. (2011a). Standardization and Quality Control of Herbal Extracts and Products. In *Traditional Herbal Medicine Research Methods* (pp. 377-427): John Wiley & Sons, Inc.

Zeng, J.-g., Tan, M.-l., Peng, X., and Luo, Q. (2011b). Standardization and Quality Control of Herbal Extracts and Products. In W. J. H. Liu (Ed.), *Traditional Herbal Medicine Research Methods: Identification, Analysis, Bioassay, and Pharmaceutical and Clinical Studies*. Hoboken, NJ, USA: John Wiley & Sons, Inc.

Zhang, H. H., Huang, J., Düvel, K., Boback, B., Wu, S., Squillace, R. M., et al. (2009). Insulin Stimulates Adipogenesis through the Akt-TSC2-mTORC1 Pathway. *PLOS ONE, 4*(7), e6189.

Zhang, X. F., and Tan, B. K. (2000). Anti-diabetic property of ethanolic extract of Andrographis paniculata in streptozotocin-diabetic rats. *Acta Pharmacol Sin, 21*(12), 1157-1164.

Zhao, S., Huang, J., and Ye, J. (2015). A fresh look at zebrafish from the perspective of cancer research. *Journal of Experimental & Clinical Cancer Research, 34*(1), 1-9.

Ziv, L., Muto, A., Schoonheim, P. J., Meijsing, S. H., Strasser, D., and Ingraham, H. A. (2013). An affective disorder in zebrafish with mutation of the glucocorticoid receptor. *Mol Psychiatry, 18*.