UNIVERSITI PUTRA MALAYSIA

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

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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 Master of Science

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

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March 2013

Chairman: Professor Amin Ismail, PhD

Faculty: Medicine and Health Sciences

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

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

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

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

Oleh

NURUL NADIRAH BINTI MOKIRAN

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

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

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I certify that a Thesis Examination Committee has met on 27 March 2014 to conduct the final examination of Nurul Nadirah binti Mokiran on her thesis entitled "Effects of Dabai (*Canarium odontophyllum* Miq.) Fruit Extract on Biochemical Parameters of Obese-Diabetic Rats" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the Master of Science.

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LIST OF ABBREVIATIONS / ANNOTATIONS

AAPH	2,2’-azobis(2-methylpropionamidine) dihydrochloride
ABTS	2,2'-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid)
ACUC	Animal Care and Use Committee
ADP	Adenosine diphosphate
AGEs	Glycation end-products
ANOVA	Analysis of variance
apoA-1	Apolipoprotein A-1
ATP	Adenosine triphosphate
AUC	Area under curve
BHT	Butylated hydroxytoluene
BMI	Body mass index
BW	Body weight
CVD	Cardiovascular disease
DAD	Diode array detector
DPPH	2,2-diphenyl-1-picrylhydrazyl
DPP-IV	dipeptidyl peptidase IV
EDTA	Ethylenediaminetetraacetic acid
ESI	Electron spray ionization
ESRD	End-stage renal disease
GAE	Gallic acid equivalent
GDM	Gestational diabetes mellitus
GLP-1	glucagon-like peptide-1
GLUT4	glucose transporter type 4
GR	Glutathione Reductase
GPx	Glutathione peroxidase
GSH	Glutathione
GSSG	Oxidised glutathione
H^+	Hydrogen
H_2O	Water
HCl	Hydrochloric acid
HDL	High-density lipoprotein
HLA	Human leukocyte antigen
HPLC	High-performance liquid chromatography
H_2O_2	Hydrogen peroxide
HOMA-IR	Homeostatic model assessment of Insulin resistance
IC_{50}	Inhibition concentration to scavenge 50% of radical
IDDM	Insulin-dependent diabetes mellitus
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
LDL	Low-density lipoprotein
LPC	Lysophosphatidylcholine
LPL	Lipoprotein lipase
Mg^{2+}	Magnesium
MW	Molecular weight
NaCl	Sodium chloride
NADPH	Reduced nicotinamide adenine dinucleotide phosphate
NHMS	National Health Morbidity Survey
NIDDM	Non-insulin dependant diabetes mellitus

NEFAs	Non-esterified fatty acids
NO	Nitric oxide
O_2	Oxygen
OGTT	Oral glucose tolerance test
ORAC	Oxygen radical absorbance capacity
PC	Phosphatidylcholine
PPAR	Peroxisome proliferator-activated receptor
pPLA2	Phospholipase A2
ROS	Reactive oxygen species
SD	Standard deviation
SEM	Standard error of means
SOD	Superoxide dismutase
SPSS	Statistic package for social sciences
STZ	Streptozotocin
Su's	Sulfonylureas
TAS	Total antioxidant status
TMB	3,3',5,5'-tetramethylbenzidine
T1DM	Type-1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TNF	Tumor necrosis factor
t_R	Retention time
Tzd's	Thiazolidinediones
UCP	Uncoupling proteins
UK	United Kingdom
UV	Ultraviolet
Vis	Visible
WHO	World Health Organization

CHAPTER 1

INTRODUCTION

1.1 Research Background

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

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

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

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

1.2 Statements of Problem

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

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

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

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

1.3 Significance of the Study

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

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

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

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

1.4 Objectives

1.4.1 General Objective

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

1.4.1 Specific objectives

1. To determine the antioxidant activity (DPPH, BCB and ORAC assay) and polyphenol profile of *dabai* extract by using HPLC.

2. To determine the effect of *dabai* extract on body weight, BMI, food and water intake of obese-diabetic rats.

3. To evaluate the effect of *dabai* extract on plasma glucose level, oral glucose tolerance test (OGTT), lipid profile (total cholesterol, triglyceride, HDL-c and LDL-c) and insulin profile (insulin level, sensitivity and resistance) on obese-diabetic rats.

4. To determine the effect of *dabai* extract on endogenous total antioxidant status (TAS) and antioxidant enzymes, glutathione peroxidase (GPx) and superoxide dismutase (SOD) activities in obese-diabetic rats.

REFERENCES

Acharya, J. D. and Ghaskadbi, S. (2010). Islets and their antioxidant defense. *Islets*. 2: 225-235.

Achenbach, P., Bonifacio, E., Koczwara, K. and Ziegler, A. G. (2005). Natural history of type 1 diabetes. *Diabetes.* 54; S25–S31.

Akanitapichat, P., Phraibung, K., Nuchklang, K., and Prompitakkul, S. 2010. Antioxidant and hepatoprotective activities of five eggplant varieties. *Food and Chemical Toxicology*. 48: 3017–3021.

Alberti, K. G. and Zimmet, P. Z. (1998). Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabetic Medicine.* 15: 539–553.

Aljadi, A. M. and Yusoff, K. M. (2003).Isolation and identification of phenolic acids in Malaysian honey with antibacterial properties. *Turkish Journal of Medical Sciences*. 33: 229-236.

American Diabetes Association. Diabetes Facts. Alexandria, VA, 1998

Ann, M. A., David, E. J. and James, M. F. (2005). Evaluation and prevention of diabetic neuropathy. *American Family Physician*.71: 2123-2128.

Andres, A., Donovan, S. M. and Kuhlenschmidt, M. S. (2009). Soy isoflavones and virus infections. *The Journal of Nutritional Biochemistry*. 20: 563–569.

Andrikopoulos, N. K., Kaliora, A. C., Assimopoulou, A. N. and Papageorgiou, V. P. (2002). Inhibitory activity of minor polyphenolic and nonpolyphenolic constituents of olive oil against in vitro low-density lipoprotein oxidation. *Journal of Medicinal Food*. 5: 1–7.

Arvouet-Grand, A., Vennat, B., Pourrat, A., and Legret, P. (1994). Standardisation dun extrait de propolis et identification des principaux constituants. *Journal de Pharmacie de Belgique*. 49: 462–468.

Atkinson, M. A and Eisenbarth, G. S. (2001). Type I diabetes mellitus. New perspectives on disease pathogenesis and treatment. *Lancet*. 358: 221–229.

Azlan, A., Mohamad Nasir, N. N., Amom, Z. and Ismail, A. (2009). Physical properties of skin, flesh, and kernel of *Canarium odontophyllum* fruit. *Journal of Food, Agriculture & Environment*. 7: 55–57.

Azlan, A., Prasad, K. N., Khoo, H. E., Abdul-Aziz, N., Mohamad, A., Ismail, A., Amom, Z. (2010). Comparison of fatty acids, vitamin E and physicochemical

properties of *Canarium odontophyllum* Miq. (dabai), olive and palm oils. *Journal of Food Composition and Analysis*. 23: 772-776.

Azrina, A., Nurul Nadiah, M. N. and Amin, I. (2010). Antioxidant properties of methanolic extract of *Canarium odontophyllum* fruit. *International Food Research Journal*. 17: 319-326.

Bach, J. F. (1994). Insulin-dependent diabetes mellitus as an autoimmune disease. *Endocrine Review*. 15: 516–542.

Bagchi, D., Sen, C. K., Ray, S. D., Das, D. K., Bagchi, M., Preuss, H. G. and Vinson J. A. (2003). Molecular mechanisms of cardioprotection by a novel grape seed proanthocyanidin extract. *Mutation Research*. (523–524): 87–97.

Bagchi, D., Sen, C. K., Bagchi, M. and Atalay, M. (2004). Anti-angiogenic, antioxidant, and anti-carcinogenic properties of a novel anthocyanin-rich berry extract formula. *Biochemistry (Moscow)*. 69: 75-80.

Bailey, C. J. And Turner, R.C. (1996). Metformin. *The New England Journal of Medicine*. 334: 574-579.

Balasubashini, M., Rukkumani, R., Viswanathan, P. and Menon, V. P. (2004). Ferulic acid alleviates lipid peroxidation in diabetic rats. *Phytotherapy Research*. 18: 310–314.

Bailey, C. J. and Turner, R.C. (1996). Metformin. *The New England Journal of Medicine*. 334: 574-579.

Bansal, P., Paula, P., Mudgal, J., Nayak, P. G., Pannakal, S. T., Priyadarsini, K. I. and Unnikrishnan, M. K. (2012). Antidiabetic, antihyperlipidemic and antioxidant effects of the flavonoid rich fraction of Pilea microphylla (L.) in high fat diet/streptozotocin-induced diabetes in mice. *Experimental and Toxicologic Pathology*. 64: 651– 658.

Barreiera, J. C. M., Ferreira, I. C. F. R., Oliveira, M. B. P. P. and Pereira, J. A. (2008). Antioxidant activities of the extracts from chestnut flower, leaf, skins and fruit. *Food Chemistry*. 107: 1106–1113.

Baynes, J. W. and Thorpe, S. R. (1999). Role of oxidative stress in diabetic complications: A new perspective on an old paradigm. *Diabetes*. 48: 1–9.

Bazzano, L.A., Serdula, M. K. and Liu, S. 2003. Dietary intake of fruits and vegetables and risk of cardiovascular disease. *Current Atherosclerosis Reports*. 5: 492–499.

Beard, H. A., Al Ghatrif, M., Samper-Ternent, R., Gerst, K. and Markides, K. S. (2009). Trends in diabetes prevalence and diabetes-related complications in older Mexican Americans from 1993–1994 to 2004 –2005. *Diabetes Care*. 32: 2212-2217.

Boden, G. (1997). Role of fatty acids in the pathogenesis of insulin resistance and NIDDM. *Diabetes*. 46: 3-10.

Boulton, A. J. M., Vileikyte, L., Ragnarson-Tennvall, G. and Apelqvist, J. (2005). The global burden of diabetic foot disease. *The Lancet*. 366: 1719-1724.

Boyko, E. J., Fujimoto, W. Y., Leonetti, D. L. and Newell-Morris, L.(2000). Visceral Adiposity and Risk of Type 2 Diabetes. *Diabetes Care*. 23: 465–471.

Boyle, J. P., Thompson, T. J., Barker, L. E. and Williamson, D. (2010). Projection of the year 2050 burden of diabetes in the US adult population: dynamic modeling of incidence, mortality, and prediabetes prevalence. *Population Health Metrics*. 8: 1-12.

Bursill, C. A., Abbey, M. and Roach, P. D. (2007). A green tea extract lowers plasma cholesterol by inhibiting cholesterol synthesis and upregulating the LDL receptor in the cholesterol-fed rabbit. *Atherosclerosis*. 193: 86-93.

Bylund, A., Saarinen, N., Zhang, J. X., Bergh, A., Widmark, A., Johansson, A., Lundin, E., Adlercreutz, H., Hallmans, G., Stattin, P. and Makela, S. (2005). Anticancer effects of a plant lignan 7-hydroxymatairesinol on a prostate cancer model *in-vivo*. *Experimental Biology and Medicine*. 230: 217-223.

Cadenas, E. (1997). Basic mechanisms of antioxidant activity. *Biofactors*. 6: 391–397.

Cano, A., Garcia-Perez, M. A. and Tarin, J. J. (2010). Isoflavones and cardiovascular disease. *Maturitas*. 67: 219–226.

Carlos, J. T and Dawes, S. N. (1990). South Pacific tropical nut cultivation: status and outlook. Institute of Research Extension and Training, University of the South Pacific, Apia, Western Samoa.

Carter, J. S., Pugh, J. A. and Monterrosa, A. (1996). Non-insulin-dependent diabetes mellitus in minorities in the United States. *Annals of Internal Medicine*. 125: 221-232.

Chai, C.C., Teo, G.K., Lau, C.Y. and Pawozen, A. M. A. (2008). Conservation and sustainable utilization of indigenous vegetables of Sarawak. In: Agrobiodiversity in Malaysia. Malaysian Agriculture Research and Development Institute, Serdang, Malaysia, pp. 47–55.

Chang, W. H. and Liu, J. F. (2009). Effects of kiwi fruit consumption on serum lipid profiles and antioxidative status in hyperlipidemic subjects. *International Journal of Food Sciences and Nutrition*, 60: 709–716.

Chavez, M., Seeley, R. J., Havel, P. J., Friedman, M. I., Matson, C. A., Woods, S. C. and Schwartz, M. W. (1998). Effect of a high-fat diet on food intake and hypothalamic neuropeptide gene expression in streptozotocin diabetes. *Journal of Clinical Investigation*. 102: 340–346.

Chew, Y. L., Lim, Y. Y. and Khoo, K.S. (2008). Antioxidant activity of three edible seaweeds from two areas in South East Asia. *LWT-Food Science and Technology*. 41: 1067–1072.

Chew, L. Y., Prasad, K. N., Amin, I., Azrina, A. and Lau, C. Y. (2011). Nutritional composition and antioxidant properties of *Canarium odontophyllum* Miq. (dabai) fruits. *Journal of Food Composition and Analysis*. 24: 670–677.

Chew, L. Y., Khoo, H. E., Amin, I., Azrina, A. and Lau, C. Y. (2012). Analysis of phenolic compounds of dabai (*Canarium odontophyllum* Miq.) fruits by high-performance liquid chromatography. *Food Analytical Methods*. 5: 126–137.

Chiang, L. C., Ng, L. T., Lin, I. C., Kuo, P. L. and Lin, C.C. (2006). Anti-proliferative effect of apigenin and its apoptotic induction in human Hep G2 cells. *Cancer Letters*. 237: 207–214.

Cleland, S. J., Petrie, J. R., Small, M., Elliott, H. L. and Connell, J. M. (2003). Insulin action is associated with endothelial function in hypertension and type 2 diabetes. *Hypertension*. 35: 507-511.

Cox, S. L. (2004). Rosiglitazone maleate/metformin hydrochloride: a new formulation therapy for type 2 diabetes. *Drugs Today (Barc)*. 40: 633–643.

Daisy, P., Balasubramaniam, K., Rajalakshmi, M., Eliza, J. and Selvaraj, J. (2010). Insulin mimetic impact of catechin isolated from *Cassia fistula* on the glucose oxidation and molecular mechanisms of glucose uptake on streptozotocin-induced diabetic Wistar rats. *Phytomedicine*. 17: 28–36.

Danda, R. S., Habiba, N. M., Rincon-Choles, H., Bhandari, B. K., Barnes, J. L., Abboud, H. E. and Pergola, P. E. (2005). Kidney involvement in a nongenetic rat model of type 2 diabetes. *Kidney International*. 68: 2562–2571.

Daousi, C., Casson, I. F., Gill, G. V., MacFarlane, I. A., Wilding, J. P. H. and Pinkney, J. H. (2006). Prevalence of obesity in type 2 diabetes in secondary care: association with cardiovascular risk factors. *Postgraduate Medical Journal*. 82: 280-284.

Davis, W. A., Norman, P. E., Bruce, D. G. and Davis, T. M. E. (2006). Predictors, consequences and costs of diabetes-related lower extremity amputation complicating type 2 diabetes: The Fremantle Diabetes Study. *Diabetologia*. 49: 2634-2641.

Deby, C. and Goutier, R. (1990). New perspectives on the biochemistry of superoxide anion and the efficiency of superoxide dismutases. *Biochemical and Pharmacology*. 39: 399–405.

De Souza Schmidt Goncalves, A. E., Lajolo, F. M. and Genoves, M. I. (2010). Chemical composition and antioxidant/antidiabetic potential of Brazilian native fruits and commercial frozen pulps. *Journal of Agricultural and Food Chemistry*. 58: 4666–4674.

Dewanjee, S., Das, A. K., Sahu, R. and Gangopadhyay, M. (2009). Antidiabetic activity of *Diospyros peregrina* fruit: Effect on hyperglycemia, hyperlipidemia and

augmented oxidative stress in experimental type 2 diabetes. *Food and Chemical Toxicology*. 47: 2679–2685.

Diakogiannaki, E., Dhayal, S., Childs, C.E., Calder, P.C., Welters, H.J. and Morgan, N.G. (2007). Mechanisms involved in the cytotoxic and cytoprotective actions of saturated versus monounsaturated long chain fatty acids in pancreatic β-cells. *Journal of Endocrinology*. 194: 283–291.

Droge, W. (2002). Free Radicals in the Physiological Control of Cell Function. *Physiological Review*. 82: 47-95.

Duby, J. J., Campbell, R. K., Setter, S. M., White, J. R. and Rasmussen, K. A. (2004) Diabetic neuropathy: an intensive review. *American Journal of Health-System Pharmacy*. 61: 160–173.

Dudonne, S., Vitrac, X., Coutiere, P., Woillez, M. and Merillon, J. M. (2009). Comparative study of antioxidant properties and total phenolic content of 30 plant extracts of industrial interest using DPPH, ABTS, FRAP, SOD, and ORAC assays. *Journal of Agricultural and Food Chemistry*. 57: 1768–1774.

Egede, L. E., Ye, X., Zheng, D. and Silverstein, M. D. (2002). The prevalence and pattern of complementary and alternative medicine use in individuals with diabetes. *Diabetes Care.* 25: 324–329.

Engelgau, M. M., Geiss, L. S., Saaddine, J. B., Boyle, J. P., Benjamin, J. M., Gregg, E. W., Tierney, E. F., Rios-Burrow, N. Mokdad, A. H., Ford, E. S., Imperatore, G. And Narayanan, K. M. V. (2004). The evolving diabetes burden in the United States. *Annals of Internal Medicine*. 140: 945-950.

Ehlenfeldt, M. K. and Prior, R. L. (2001). Oxygen radical absorbance capacity (ORAC) and phenolic and anthocyanin concentrations in fruit and leaf tissues of highbush blueberry. Journal of Agricultural and Food Chemistry. 49: 2222−2227.

Erlund, I., Koli, R., Alfthan, G., Marniemi, J., Puuka, P., Mustonen, P., Mattila, P. and Jula, A. (2008). Favorable effects of berry consumption on platelet function, blood pressure, and HDL cholesterol. *The American Journal of Clinical Nutrition*. 87: 323–331.

Evans, J. L., Goldfine, I. D., Maddux, B. A. and Grodsky, G. M. (2003). Are oxidative stress-activated signaling pathways mediators of insulin resistance and β-cell dysfunction? *Diabetes*. 52: 1–8.

Ezzati, M., Lopez, A., Rodgers, A., Vander Hoorn, S., Murray, C. And the comparative risk assessment collaborating group. (2002). Selected major risk factors and global and regional burden of disease. *The Lancet*. 360: 1347-1360

Feig, D. S., Zinman, B., Wang, X. and Hux, J. E. (2008). Risk of development of diabetes mellitus after diagnosis of gestational diabetes. *Canadian Medical Association Journal*. 179: 229-234.

Fisher, N. D., Hughes, M., Gerhard-Herman, M. and Hollenberg, N. K. (2003). Flavanol rich cocoa induces nitric-oxide-dependent vasodilation in healthy humans. *Journal of Hypertension*. 21: 2281–2286.

Fong, D. S., Aiello, L., Gardner, T. W., King, G. L., Blankenship, G., Cavallerano, J. D., Ferris, F. L. and Klein, R. (2004). Retinopathy in diabetes. *Diabetes Care*. 27: S84-S87.

Fonseca, V. A. 2006. Chapter 23: Insulin Secretagogues. pg 262-280. Clinical Diabetes: Translating research into practice. Philadelphia, Elsevier, 1st edition.

Friedman, M., Henika, P. R., Levin, C. E., Mandrell, R. E. and Kozukue, N. (2006). Antimicrobial activities of tea catechins and theaflavins and tea extracts against *Bacillus cereus. Journal of Food Protection*. 69: 354-361.

Frydoonfar, H. R., McGrath, D. R. and Spigelman, A. D. (2003). The variable effect on proliferation of a colon cancer cell line by the citrus fruit flavonoid naringenin. *Colorectal Disease.* 5: 149–152.

Fukumitsu, S., Aida, K., Ueno, N., Ozawa, S., Takahashi, Y. and Kobori M. (2008). Flaxseed lignan attenuates high-fat diet-induced fat accumulation and induces adiponectin expression in mice. *British Journal of Nutrition*. 100: 669–676.

Gbolade, A. A. (2009). Inventory of antidiabetic plants in selected districts of Lagos State, Nigeria. *Journal of Ethnopharmacology.* 121: 135–139.

Giacco, F. and Brownlee, M. (2010). Oxidative stress and diabetic complications. *Circulation Research*. 107: 1058-1070.

Goh, S. Y. and Cooper, M. E. (2008). The role of advanced glycation end products in progression and complications of diabetes. *Journal of Clinical Endocrinology & Metabolism*. 93: 1143–1152.

Goldberg, R. B. (2003). Cardiovascular disease in patients who have diabetes. *Cardiology Clinics*. 21: 399–413.

Garcia-Lafuente, Guillamon, E., Villaris, A., Rostagno, M. A. and Martinez, J. A. (2009). Flavonoids as anti-inflammatory agents: implications in cancer and cardiovascular disease. *Inflammatory Research*. 58: 537-552.

Goldstein, B. J. and Muller-Wieland, D. 2003. Textbook of type 2 diabetes, pg 253-260. Martin Dunitz Ltd, United Kingdom, 1st edition.

Gross, J. L., de Azevedo, M. J., Silveiro, S. P., Canani, L. H., Caramori, M. L. and Zelmanovitz, T. (2005). Diabetic nephropathy : diagnosis, prevention, and treatment. *Diabetes Care*. 28: 164-176.

Gulati, N., Laudet, B., Zohrabian, V. M., Murali, R. and Jhanwar-Uniyal, M. (2006). The Antiproliferative Effect of Quercetin in Cancer Cells is Mediated via Inhibition of the PI3K-Akt/PKB Pathway. *Anticancer Research*. 26: 1177-1182 .

Guillou, H., Martin, P. G. and Pineau, T. (2008). Transcriptional regulation of hepatic fatty acid metabolism. *Subcellular Biochemistry*. 49: 3–47.

Hamalainen, M., Nieminen, R., Vuorela, P., Heinonen, M. and Moilanen, E. (2007). Anti-inflammatory effects of flavonoids: genistein, kaempferol, quercetin, and daidzein inhibit stat-1 and nf-κb activations,whereas flavone, isorhamnetin, naringenin, and pelargonidin inhibit only NF-κB activation along with their inhibitory effect on iNOS expression and NO production in activated macrophages. *Mediators of Inflammation*. 45673: 1-12.

Hamauzu, Y., Yasui, H., Inno, T., Kume, C. and Midori, O. (2005). Phenolic profile, antioxidant property, and anti-influenza viral activity of Chinese quince (*Pseudocydonia sinensis* Schneid.), quince (*Cydonia oblonga* Mill.), and apple (*Malus domestica* Mill.) fruits. *Journal of Agricultural and Food Chemistry*. 53: 928−934.

Harborne, J. B. and Williams, C. A. (2000). Advances in flavonoid research since 1992. *Phytochemistry*. 55: 481–504.

Harmon, J. S., Bogdani, M., Parazzoli, S. D., Mak, S. S. M., Oseid, E. A., Berghmans, M., LeBoeuf, R. C. and Paul Robertson, R. (2009). β-cell-specific overexpression of glutathione peroxidase preserves intranuclear MafA and reverses diabetes in db/db mice. *Endocrinology*. 150: 4855– 4862.

Hariri, N. and Thibault. L. (2010). High-fat diet-induced obesity in animal models. *Nutrition Research Reviews*. 23: 270–299.

He, Z. and Xia, W. (2007). Analysis of phenolic compounds in Chinese olive (*Canarium album* L.) fruit by RPHPLC–DAD–ESI–MS. *Food Chemistry.* 105; 1307–1311.

Harris, M. I., Klein, R., Welborn, T. A. and Knuiman, M, W. (1992). Onset of NIDDM occurs at least 4-7 yr before clinical diagnosis. *Diabetes Care*. 15: 815-819.

Hirschberg, Y., Karara, A. H., Pletrl, A. O., McLeod, J. F. (2000). Improved control of mealtime glucose excursions with coadministration of nateglinide and metformin. *Diabetes Care*. 23: 349-353.

Hodgson, E. K. and Fridovich, I. (1975). The interaction of bovine erythrocyte superoxide dismutase with hydrogen peroxide: inactivation of the enzyme. *Biochemistry*. 24: 5294–5299.

Homan, R. and Hamelehle, K. L. (1998). Phospholipase A2 relieves phosphatidylcholine inhibition of micellar cholesterol absorption and transport by human intestinal cell line Caco-2. *Journal of Lipid Research*. 39: 1197-1209.

Hong, H., Landauer, M. R., Foriska, M. A. and Ledney, G. D. (2006). Antibacterial activity of the soy isoflavone genistein. *Journal of Basic Microbiology*. 46: 329–335.

Hossain, P., Kawar, B. and El Nahas, M. (2007).Obesity and diabetes in the developing world — A growing challenge. *The New England Journal of Medicine*. 356: 213-215.

Huang, D., Boxin, O. U. and Prior, R. L. (2005). The chemistry behind antioxidant capacity assays. *Journal of Agricultural and Food Chemistry*. 53: 1841–1856.

Huang, R., Mendis, E. and Kim, S. K. (2005). Factors affecting the free radical scavenging behavior of chitosan sulphate. *International Journal of Biological Macromolecules*. 36: 120–127.

Hu, F. B., Manson, J. E., Stampfer, M. J., Colditz, G. and Liu S. (2001). Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. *The New England Journal of Medicine*. 345: 790-797.

Hussain, A., Claussen, B., Ramachandran, A. and William, R. (2007). Prevention of type 2 diabetes: A review. *Diabetes Research and Clinical Practice* 76: 317–326.

Icks, A., Haastert, B., Trautner, C., Giani, G., Glaeske, G. and Hoffmann, F. (2009). Incidence of lower-limb amputations in the diabetic compared to the non-diabetic population. findings from nationwide insurance data, Germany, 2005-2007. *Experimental and Clinical Endocrinology & Diabetes*. 117: 500-504.

Ikarashi, N., Toda, T., Okinawa, T., Ito, K., Ochiai, W. and Sugiyama, K. (2011). Anti-obesity and anti-diabetic effects of acacia polyphenol in obesediabetic KKAy mice fed high-fat diet. *Evidence-Based Complementary and Alternative Medicine*. 952031: 1-10.

Ikeda, I., Kobayashi, M., Hamada, T., Tsuda, K., Goto, H., Imaizumi, K., Nozawa, A., Sugimoto, A. And Kakuda, T. (2003). Heat-epimerized tea catechins rich in gallocatechin gallate and catechin gallate are more effective to inhibit cholesterol absorption than tea catechins rich in epigallocatechin gallate and epicatechin gallate. *Journal of Agricultural and Food Chemistry*. 51: 7303-7307.

Inoue, M., Ohtake, T., Motomura, W., Takahashi, N., Hosoki, Y., Miyoshi, S., Suzuki, Y., Saito, H., Kohgo, Y. and Okumura, T. (2005). Increased expression of PPAR gamma in high fat diet-induced liver steatosis in mice. *Biochemical and Biophysical Research Communication*. 336: 215–22.

International Diabetes Federation. IDF Diabetes Atlas, 4th ed., Brussels, Belgium: International Diabetes Federation, 2009.

Inzucchi, S. E. (2002). Oral antihyperglycemic activity therapy for type 2 diabetes. Scientific Review and Clinical Application. *The Journal of the American Medical Association*. 287: 360-372.

Jalil, A. M. M., Ismail, A., Chong, P. P., Hamid, M. and Syed Kamaruddin, S. H. (2009). Effects of cocoa extract containing polyphenols and methylxanthines on

biochemical parameters of obese-diabetic rats. *Journal of the Science of Food and Agriculture*. 89: 130-137.

Jandacek, R. J. 2000. The canary in the cell: A sentinel role for β-carotene. *Journal of Nutrition*. 130: 628-665.

Jayaprakasha, G. K., Singh, R. P. and Sakariah, K. K. (2001). Antioxidant activity of grape seed (*Vitis vinifera*) extracts on peroxidation models *in vitro*. *Food Chemistry*. 73: 285–290.

Jia, J., Zhang, X., Hua, Y. S., Wua, Y., Wang, Q. Z., Li, N. N., Guo, Q. C. and Dong, X. C. (2009). Evaluation of in vivo antioxidant activities of *Ganoderma lucidum* polysaccharides in STZ-diabetic rats. *Food Chemistry*. 115: 32–36.

Johansen, K. (1999). Efficiacy of metformin in the treatment of NIDDM: meta-analysis. *Diabetes Care*. 22: 33-37.

Ju, J. B., Kim, J. S., Choi, C. W., Lee, H. K., Oha, T. K. and Kim, S. C. (2008). Comparison between ethanolic and aqueous extracts from Chinese juniper berries for hypoglycaemic and hypolipidemic effects in alloxan-induced diabetic rats. *Journal of Ethnopharmacology* . 115: 110–115.

Jung, E. H, Kim, S. R., Hwang, I. K. and Ha, T. Y. (2007). Hypoglycemic effects of a phenolic acid fraction of rice bran and ferulic acid in C57BL/KsJ-db/db mice. *Journal of Agricultural and Food Chemistry*. 55: 9800–9804.

Jurgoński, A., Juśkiewicz, J. and Zduńczyk, Z. (2008). Ingestion of black chokeberry fruit extract leads to intestinal and systemic changes in a rat model of prediabetes and hyperlipidemia. Plant Foods in Human Nutrition. 63; 176–182.

Kadowaki, T., Yamauchi, T., Kubota, N., Hara, K., Ueki, K. and Tobe, K. (2006). Adiponectin and adiponectin receptors in insulin resistance, diabetes, and the metabolic syndrome. *Journal of Clinical Investigation*. 116: 1784–1792.

Kahn, S. E. (2001). the importance of β-cell failure in the development and progression of type 2 diabetes. *The Journal of Clinical Endocrinology & Metabolism*. 86: 4047–4058.

Karim, M., McCormick, K. and Kappagoda, C. T. (2000). Effects of cocoa extracts on endothelium-dependent relaxation. *Journal of Nutrition*. 130: S2105–2108.

Katsuki, A., Sumida, Y., Gabazza, E. C., Furuta, M., Araki-Sasaki, R., Hori, Y. and Yano, Y., Adachi, Y. (2001). Homeostasis model assessment is a reliable indicator of insulin resistance during follow-up of patients with Type 2 Diabetes. *Diabetes Care*. 24: 362–365.

Kawada, M., Ohno, Y., Ri, Y., Ikoma, T., Yuugetu, H., Asai, T., Watanabe, M., Yasuda, N., Akao, S., Takemura, G., Minatoguchi, S., Gotoh, K., Fujiwara, H. and Fukuda, K. (2001). Anti-tumor effect of gallic acid on LL-2 lung cancer cells transplanted in mice. *Anti-Cancer Drugs*. 12: 847-852.

Kelly, I. E., Han, T. S., Walsh, K. and Lean, M. E. (1999). Effect of a thiazolidinedione compound on body fat and fat distribution of patient with type 2 diabetes. *Diabetes Care*. 22: 288-293.

Kevers, C., Falkowski, M., Tabart, J., Defraigne, J. O., Dommes, J. and Pincemail, J. (2007). Evolution of antioxidant capacity during storage of selected fruits and vegetables. Journal of Agricultural and Food Chemistry. 55: 8596–8603.

Khosla, P., Gupta, D. and Nagpal, R. K. (1995). Effect of *Trigonella foenum graecum* (fenugreek) on serum lipids in normal and diabetic rats. *Indian Journal of Pharmacology*. 27: 89–93.

Khoo, H. E., Azlan, A., Ismail, A. and Abas, Faridah. (2011). Influence of different extraction media on phenolic contents and antioxidant capacity of defatted dabai (*Canarium odontophyllum*) fruit. *Food Analytical Methods*. 5: 339-350.

Kikkawa, R., Koya, D. and Haneda, M. (2003). Progression of diabetic nephropathy. *American Journal of Kidney Diseases*. 41: S19–S21.

Kim, J. K., Fillmore, J. J., Chen, Y., Yu, C., Moore, I. K., Pypaert, M., Peer Lutz, E., Kako, Y., Velez-Carrasco, W., Goldberg, I. J., Breslow, J. L. and Shulman, G. I. (2001). Tissue-specific overexpression of lipoprotein lipase causes tissue-specific insulin resistance. *Proceeding of the National Academy of Sciences of the United States of America*. 98: 7522–7527.

Kim, H. K., Nelson-Dooley, C., Della-Fera, M. A., Yang, J. Y., Zhang, W., Duan, J., Hartzell, D. L., Hamrick, M. W. and Baile, C. A. (2006). Genistein decreases food intake, body weight, and fat pad weight and causes adipose tissue apoptosis in ovariectomized female mice. *Journal of Nutrition*. 136: 409–414.

King, H., Aubert, R. E. and Herman, W. H. (1998). Global Burden of Diabetes, 1995-2025, Prevalence, numerical estimates, and projections. *Diabetes Care*. 21: 1414-1431.

Knip, M. and Siljander, H. (2008). Autoimmune mechanisms in type 1 diabetes. *Autoimmunity Reviews*. 7: 550–557.

Kolata, G. B. (1979). The phenformin ban: Is the drug an imminent hazard? *Sciences.* 203: 1094-1096.

Kole, L., Giri, B., Manna, S. K., Pal, B. and Ghosh, S. (2011). Biochanin-A, an isoflavon, showed anti-proliferative and anti-inflammatory activities through the inhibition of iNOS expression, p38-MAPK and ATF-2 phosphorylation and blocking NFκB nuclear translocation. *European Journal of Pharmacology*. 653: 8–15.

Kouambou, C. C.N., Dimo, T., Dzeufiet, P. D. D., Ngueguim, F. T., Tchamadeu, M. C., Wembe, E. F. and Kamtchouing. (2007). Antidiabetic and hypolipidemic effects of

Canarium schweinfurthii hexane bark extract in streptozotocin-diabetic rats. *Pharmacologyonline 1*: 209-219.

Kratz, J. M., Andrighetti-Frohner, C. R., Leal, P. C., Nunes, R. J., Yunes, R. A., Trybala, E., Bergstrom, T., Barardi, C. R. M. and Simoes, C. M. O. (2008). Evaluation of anti-HSV-2 activity of gallic acid and pentyl gallate. *Biological and Pharmaceutical Bulletin*. 31: 903-907.

Kumaran, A. and Karunakaran, R. J. (2006). Antioxidant and free radical scavenging activity of an aqueous extract of *Coleus aromaticus. Food Chemistry.* 97: 109–114.

Laing, S. P. Swedlow, A. J., Slater, S. D., Burden, A. C., Morris, A., Waugh, N. R., Gatling, W., Bingley, P. J. and Patterson. (2003). Mortality from heart disease in a cohort of 23,000 patients with insulin-treated diabetes. *Diabetologia*. 46: 760–765.

Latha, M., Pari, L., Sandhya, S., and Ramesh, B. (2004). Insulin secretagogue activity and cytoprotective role of the traditional antidiabetic plant *scoparia dulcis*. *Life sciences*. 75: 2007-2014.

Lamon-Fava, S. and Micherone, D. (2004). Regulation of apoA-I gene expression: mechanism of action of estrogen and genistein. *Journal of Lipid Research*. 45: 106–112.

Landis-Piwowar, K. R., Huo, C., Chen, D., Milacic, V., Shi, G., Chan, T. H. and Dou, Q. P. (2007). A Novel Prodrug of the green tea polyphenol (-)-epigallocatechin-3-gallate as a potential anticancer agent. *Cancer Research*. 67: 4303-4310.

Latha, M., Pari, L., Sandhya, S. and Ramesh, B. (2004). Insulin secretagogue activity and cytoprotective role of the traditional antidiabetic plant *Scoparia dulcis*. *Life sciences*. 75: 2007-2014.

Latiff, A., Faridah-Hanum, I. and Zakri, A.H. (2000). The importance of biodiversity conservation research and collaboration in the ASEAN : A view from Asean scientists. *In Proceedings of the First Scientific Planning Conference & Report of the Second Scientific Experts Meeting (SEC) Meeting of ARCBC*. p 24. Kuala Lumpur.

Lau, C.Y. (2009). Development of indigenous fruit crops in Sarawak: a case study on dabai fruit. *In: Proceedings of the National Conference on New Crops and Bioresources, Negeri Sembilan, Malaysia*, pp. 15–20.

Lebovitz, H. E. (1995). Diabetic ketoacidosis. *Lancet*. 345: 767—771.

Lee, J. H., Park, L. C. and Choi, J. S. (1996). The Antioxidant Activity of *Ecklonia stolonifera. Archives of Pharmacal Research*. 19; 223-227.

Lee, M. O. (1929). Determination of the surface area of the white rat with its application to the expression of metabolic results. *American Journal of Physiology*. 89: 24–33.

Leenhouts, P. W. (1959). Revision of the Burseraceae of the Malaysian area in a wider sense Xa *Canarium Stickm*. In: A Monograph of the Genus *Canarium* (Burseraceae) *Blumea*. 9: 275–475.

Lemhardi, A., Hajji, L., Michel, J. B. and Eddouks, M. (2006). Cholesterol and triglycerides lowering activities of caraway fruits in normal and streptozotocin diabetic rats. *Journal of Ethnopharmacology*. 106: 321-326.

Lenzen, S. (2008). The mechanisms of alloxan and streptozotocin-induced diabetes. *Diabetologia.* 51: 216–226.

Leslie, R. D. and Pozzilli, P. 2002. Changing Therapies for Type 2 Diabetes. pg 86-90. Martin Dunitz Ltd, United Kingdom, 1st edition.

Letchuman, G. R., Wan Nazaimoon, W. M., Wan Mohamad, W. B., Chandran, L. R., Tee, G. H., Jamaiyah, H., Isa, M. R., Zanariah, H., Fatanah, I. and Ahmad Faudzi, Y. (2010). Prevalence of diabetes in the Malaysian National Health Morbidity Survey III 2006. *Medical Journal of Malaysia*. 65: 173-179.

Lluch, A., Herbeth, B. Mejean, L. and Siest, G. (2000). Dietary intakes, eating style and overweight in the Stanislas Family Study. *International Journal of Obesity and Related Metabolic Disorder*. 24: 1493–1499.

Levin, B. E. and Dunn-Meynell, A. A. (2002). Defense of body weight depends on dietary composition and palatability in rats with diet-induced obesity. *American Journal of Physiology - Regulatory, Integrative and Comparative Physiology*. 282: R46–R54.

Levites, Y., Amit, T., Mandel, S. and Youdim, M. B. H. (2003). Neuroprotection and neurorescue against A toxicity and PKC-dependent release of nonamyloidogenic soluble precursor protein by green tea polyphenol (-)-epigallocatechin-3-gallate. *The FASEB Journal*. 17: 952-954.

Li, Y., Cao, Z. and Zhu, H. (2006). Upregulation of endogenous antioxidants and phase 2 enzymes by the red wine polyphenol, resveratrol in cultured aortic smooth muscle cells leads to cytoprotection against oxidative and electrophilic stress. *Pharmacological.* 53: 6-15.

Lipscombe, L. L. (2009). Thiazolidinediones: do harms outweigh benefits? *Canadian Medical Association Journal*. 180: 16-7.

Liu, A.H., Li, L., Xu, M., Lin, Y.H., Guo, H.Z. and Guo, D.A. (2006). Simultaneous quantification of six major phenolic acids in the roots of *Salvia miltiorrhiza* and four related traditional Chinese medicinal preparations by HPLC-DAD method. *Journal of Pharmaceutical and Biomedical Analysis*. 41: 48-56.

Liu, Y., Black, M. A., Caron, L. and Camesano, T. A. (2006). Role of cranberry juice on molecular-scale surface characteristics and adhesion behavior of *Escherichia coli*. *Biotechnology and Bioengineering*. 93: 297–305.

Luo, Q., Cai, Y., Yana, J., Sun, M. and Corke, H. (2004). Hypoglycemic and hypolipidemic effects and antioxidant activity of fruit extracts from *Lycium barbarum. Life Sciences*. 76: 137–149.

MacDonald-Wicks, L. K., Wood, L. G. and Garg, M .L. (2006). Methodology for the determination of biological antioxidant capacity in vitro: a review. *Journal of the Science of Food and Agriculture*. 86: 2046–2056.

Mämmelä, P, Savolainen, H., Lindroos, L., Kangas, J. and Vartiainen, T. (2000). Analysis of oak tannins by liquid chromatography-electrospray ionization mass spectrometry. *Journal of Chromatography A*. 891: 75–83.

Marbury, T., Huang W. C., Strange, P. and Lebowtlz, H. (1999). Repaglinide versus glyburide: a one-year comparison trial. *Diabetes Research and Clinical Practice*. 43: 155-166.

Martin, C. L., Albers, J., Herman, W. H., Cleary, P., Waberski, B., Greene, D. A., Stevens, M. J. and Feldman, E. L. (2006). Neuropathy among the Diabetes Control and Complications Trial Cohort 8 years after trial completion. *Diabetes Care*. 29: 340–344.

Meda, A., Lamien, C. E., Romito, M., Millogo, J. and Nacaoulma, O. D. (2005). Determination of the total phenolic, flavonoid and proline contents in *Burkina Fasan* honey, as well as their radical scavenging activity. *Food Chemistry*. 91: 571–57.

Mezei, O., Banz, W. J., Steger, R. W., Peluso, M. R., Winters, T. A. and Shay, N. (2003). Soy isoflavones exert antidiabetic and hypolipidemic effects through the PPAR pathways in obese zucker rats and murine RAW 264.7 Cells. *The Journal of Nutrition*. 133: 1238–1243.

Middleton, E., Kandaswami, C. and Theoharides, T. C. (2000). The effects of plant flavonoids on mammalian cells: implications for inflammation, heart disease and cancer, *Pharmacological Review*. 52: 673–751.

Mizunuma, H., Kanazawa, K., Ogura, S., Otsuka, S. and Nagai, H. (2002). Anticarcinogenic effects of isoflavones may be mediated by genistein in mouse mammary tumor virus-induced breast cancer. *Oncology*. 62:78–84.

Modak, M., Parab, P. and Ghaskadbi, S. (2009). Pancreatic islets are very poor in rectifying oxidative DNA damage. *Pancreas*. 38: 23-9.

Molyneux, P. (2003). The use of stable free radical diphenylpicrylhydrazyl (DPPH) for estimating antioxidant activity. *Journal of Science Technology*. 26: 211-219.

Moss, S. E., Klein, R. and Klein, B. E. K. (1998). The 14-year incidence of visual loss in a diabetic population. *Ophthalmology*. 105: 998-1003.

Murakami, A., Ashida, H. and Terao, J. (2008). Multitargeted cancer prevention by quercetin. *Cancer Letter*s. 269: 315–325.

Murphy, E. J., Davern, T. J., Shakil, A. O., Shick, L., Masharani, U., Chow, H., Freise, C., Lee, W. M. and Bass, N. M. (2000). Troglitazone-induced fulminant hepatic failure. Acute liver failure study group. *Digestive Diseases and Sciences*. 45: 549-553.

Murphy, K. J., Chronopoulos, A. K., Singh, I., Francis, M. A., Moriarty, H., Pike, M. J., Turner, A. H., Mann, N. J. and Sinclair, A. J. (2003). Dietary flavanols and procyanidin oligomers from cocoa (*Theobroma cacao*) inhibit platelet function. *The American Journal of Clinical Nutrition*. 77: 1466–1473.

Murussi, M., Baglio, P., Gross, J. L., Silveiro, S. P. (2002). Risk factors for microalbuminuria and macroalbuminuria in type 2 diabetic patients : a 9-year follow-up study. *Diabetes Care*. 25: 1101-1103.

Mailamani, M., Wei, J., Bhatt, S., Paul, M., Yakira, S. and Sampson, H. A. (2011). Soybean isoflavones regulate dendritic cell function and suppress allergic sensitization to peanut. *Journal of Allergy and Clinical Immunology*. 128: 1242–1250.

Nain, P., Saini, V., Sharma, S. And Nain, J. (2012). Antidiabetic and antioxidant potential of *Emblica officinalis Gaertn.* leaves. extract in streptozotocin-induced type-2 diabetes mellitus (T2DM) rats. *Journal of Ethnopharmacology*. 142: 65–7.

Nagao, T., Hase, T. and Tokimitsu, I. (2007). A green tea extract high in catechins reduces body fat and cardiovascular risks in humans. *Obesity*. 15: 1473-1483.

Nagao, T., Meguro, S., Hase, T., Otsuka, K., Komikado, M., Tokimitsu, I., Yamamoto, T. and Yamamoto, K. (2009). A catechin-rich beverage improves obesity and blood glucose control in patients with type 2 diabetes. *Obesity*. 17: 310-317.

National Health Morbidity Survey (NHMS II). Institute for Public Health. Ministry of Health Malaysia, 1996.

National Health and Morbidity Survey (NHMS III). 2006. Kuala Lumpur, Malaysia: Institute for Public Health. Ministry of Health.

National Health and Morbidity Survey 2011 (NHMS 2011). 2011. Institute for Public Health. Ministry of Health, Kuala Lumpur, Malaysia

Nestle, M. (1999). Animal v. plant foods in human diets and health: is the historical record unequivocal? *Proceedings of the Nutrition Society*. 58: 211–8.

Neu, A., Hofer, S. E., Karges, B., Oeverink, R., Rosenbauer, J. and Holl, R. (2009). Ketoacidosis at diabetes onset is still frequent in children and adolescents; a multicenter analysis of 14,664 patients from 106 institutions. *Diabetes Care*. 32: 1647–1648.

Nevenimo, T., Moxon, J., Wemin, J., Johnston, M., Bunt, C and Leakey, R. R. B. (2007). Domestication potential and marketing of *Canarium indicum* nuts in the Pacific:1. A literature review. *Agroforestry Systems*. 69:117–134.

Newton, C. A. and Raskin, P. (2004). Diabetic ketoacidosis in type 1 and type 2 diabetes mellitus; clinical and biochemical differences. *Archives of Internal Medicine*. 164: 1925-1931.

Nishikawa, H., Wakano, K. and Kitani, S. (2007). Inhibition of NADPH oxidase subunits translocation by tea catechin EGCG in mast cell. *Biochemical and Biophysical Research Communications*. 362: 504–509.

O'Leary, K. A, de Pascual-Tereasa, S., Needs, P. W., Bao, Y. P., O'Brien, N. M. and Williamson, G. (2004). Effect of flavanoids and vitamin E on cyclooxygenase-2 (COX-2) transcription. *Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis*. 551: 245–54.

Oliveira de Souza, M., Silva, M., Silva, M. E., Oliveira, R. P. and Pedrosa, M. L. (2010). Diet supplementation with acai (*Euterpe oleracea* Mart.) pulp improves biomarkers of oxidative stress and the serum lipid profile in rats. *Nutrition.* 26: 804–810.

Ono, M. and Fujimoro, K. (2011). Antiadipogenic effect of dietary apigenin through Activation of AMPK in 3T3-L1 cells. *Journal of Agricultural and Food Chemistry*. 59: 13346−13352.

Orhan, N., Berkkan, A., Orhan, D. D., Aslan, M. and Ergun, F. (2011). Effects of Juniperus oxycedrus ssp. oxycedrus on tissue lipid peroxidation, trace elements (Cu, Zn, Fe) and blood glucose levels in experimental diabetes. *Journal of Ethnopharmacology*. 133: 759–764.

Ortiz-Andrade, R. R., Sanchez-Salgado, J. C., Navarrete-Vazquez, G., Webster, S. P., Binnie, M., Garcia-Jimenez, S., Leon-Rivera, I., Cigarroa-Vazquez, P., Villalobos, R. and Estrada-Soto, S. (2008). Antidiabetic and toxicological evaluations of naringenin in normoglycaemic and NIDDM rat models and its implications on extra-pancreatic glucose regulation. *Diabetes, Obesity and Metabolism*. 10: 1097–1104.

Ou, B., Hampsch-Woodill, M. and Prior, R. L. (2001). Development and validation of an improved oxygen radical absorbance capacity assay using fluorescein as the fluorescent probe. *Journal of Agricultural and Food Chemistry*. 49; 4619−4626.

Ovalle, F. and Bell, D. S. (2002). Clinical evidence of thiazolidinedione-induced improvement of pancreatic beta-cell function in patients with type 2 diabetes mellitus. *Diabetes, Obesity and Metabolism*. 4: 56–59.

Paixao, N., Perestrelo, R., Marques, J. C. and Camara, J. S. 2007. Relationship between antioxidant capacity and total phenolic content of red, rose and white wine. *Food Chemistry*. 105: 204-214.

Porta, M. and Bandello, F. (2002). Diabetic retinopathy: a clinical update. *Diabetologia.* 45: 1617–1634.

Paredes, A., Alzuru, M., Mendez, J. and Rodriguez-Orteg, M. (2003). Anti-Sindbis Activity of Flavanones Hesperetin and Naringenin. *Biological and Pharmaceutical Bulletin*. 26: 108-109.

Prasad, K. N., Chew, L. Y., Khoo, E. K., Kong, K. W., Azlan, A. and Ismail, A. (2010). Antioxidant capacities of peel, pulp and seed fractions of *Canarium odontophyllum* Miq. Fruit. *Journal of Biomedicine and Biotechnology*. doi:10.1155/2010/871379.

Prasad, K. N., Chew, L. Y., Khoo, H. E., Yang, B., Azlan, A. and Ismail, A. (2011). Caretenoids and antioxidant capacities from *Canarium odontophyllum* Miq. fruit. *Food Chemistry*. 124: 1549–1555.

Puupponen-Pimia, R., Nohynek, L., Hartmann-Schmidlin, S., Kahkonen, M., Heinonen, M., Maatta-Riihinen, K. and Oksman-Caldentey, K. M. (2005). Berry phenolics selectively inhibit the growth of intestinal pathogens. *Journal of Applied Microbiology*. 98: 991–1000.

Rajasekaran, S., Sivagnanam, K. and Subramaniam. (2005). Antioxidant effect of *Aloe vera* gel extract in streptozotocin-induces diabetic rats. *Pharmacological Reports*. 57: 90-96.

Rajkumar, L., Srinivasan, N., Balasubramanian, K. and Govindarajulu, P. (1991). Increased degradation of dermal collagen in diabetic rats. *Indian Journal of Experimental Biology*. 29; 1081–1083.

Ramachandran, B., Ravi, K., Narayanan, V., Kandaswamy, M. and Subramanian, S. (2004). Protective effect of macrocyclic binuclear oxovanadium complex on oxidative stress in pancreas of streptozotocin induced diabetic rats. *Chemico-Biological Interaction*.149: 9–21.

Reaven, G. M. (1988). Role of insulin resistance in human disease. *Diabetes.* 37; 1595-1607.

Redondo, M. J. and Eisenbarth, G. S. (2002). Genetic control of autoimmunity in type I diabetes and associated disorders. *Diabetologia.* 45: 605– 622.

Resnikoff, S., Pascolini, D., Etya'ale, D., Kocur, I., Pararajesegaram, R., Pokharel, G. P. and Mariotti, S. P. (2004). Global data on visual impairment in the year 2002. *Bulletin of the World Health Organization*. 82: 844-851.

Riboli, E. and Norat, T. (2003). Epidemiologic evidence of the protective effect of fruit and vegetables on cancer risk. *American Journal of Clinical Nutrition*. 78: 559S–569S.

Richard, T., Pawlus, A. D., Iglesias, M. L., Pedrot, E., Waffo-Teguo, P., Merillon, J. M. and Monti, J. P. (2011). Neuroprotective properties of resveratrol and derivatives. *Annals Of The New York Academy Of Sciences*. 1215: 103–108.

Ritchie, S. A. and Connell, J. M. C. (2007). The link between abdominal obesity, metabolic syndrome and cardiovascular disease. *Nutrition, Metabolism & Cardiovascular Diseases*. 17: 319-326.

Robertson, R.P. (2006). Oxidative stress and impaired insulin secretion in type 2 diabetes. *Current Opinion in Pharmacology*. 6: 615–619.

Rødtjer, A., Skibsted, L. H. and Andersen, M. L. (2006) . Antioxidative and prooxidative effects of extracts made from cherry liqueur pomace. *Food Chemistry*. 99: 6–14.

Rosak, C. (2002). The pathophysiologic basis of efficacy and clinical experience with the new oral antidiabetic agents. *Journal of Diabetes and its Complications*. 16: 123–132.

Ruzaidi, A. M. M., Abbe, M. M. J., Amin, I., Nawalyah, A. G. and Muhajir, H. (2008). Protective effect of polyphenol-rich extract prepared from Malaysian cocoa (*Theobroma cacao*) on glucose levels and lipid profiles in streptozotocin-induced diabetic rats. *Journal of the Science of Food and Agriculture*. 88; 1442–1447.

Said, G. (2007). Diabetic neuropathy- a review. *Nature Clinical Practice Neurology*. 3: 331-340.

Saltiel, A. R and Kahn, C. R. (2001). Insulin signalling and the regulation of glucose and lipid metabolism. *Nature*. 414: 799–806.

Sano, T., Oda, E., Yamashita, T., Naemuraa, A., Ijiria, Y., Yamakoshi, J. and Yamamoto, J. (2005). Anti-thrombotic effect of proanthocyanidin, a purified ingredient of grape seed. *Thrombosis Research*. 115: 115–121.

Sasaki, R., Nishimura, N., Hoshino, H., Isa, Y., Kadowaki, M., Ichi, T., Tanaka, A., Nishiumi, S., Fukuda, I., Ashida, H., Horio, F. and Tsuda, T. (2007). Cyanidin 3-glucoside ameliorates hyperglycemia and insulin sensitivity due to downregulation of retinol binding protein 4 expression in diabetic mice. *Biochemical Pharmacology*. 74: 1619–1627.

Saxena, A. K., Srivastava, P., Kale, R. K. and Baquer, N. Z. (1993). Impaired antioxidant status in diabetic rat liver. Effect of vanadate. *Biochemical Pharmacology*. 45: 539–542.

Schauss, A. G., Wu, X., Prior, R. L., Ou, B., Huang, D., Owens, J., Agarwal, A., Jensen, G. S., Hart, A. N. and Shanbrom, E. (2006). Antioxidant capacity and other bioactivities of the freeze-dried Amazonian palm berry, *Euterpe oleraceae* Mart. (Acai). *Journal of Agricultural and Food Chemistry*. 54: 8604−8610.

Scherer, P. E. 2006. Adipose tissue from lipid storage compartment to endocrine organ. *Diabetes*. 55: 1537-1545.

Schroeter, H., Heiss, C., Balzer, J., Kleinbongard, P., Keen, C. L., Hollenberg, N. K., Sies, H., Kwik-Uribe, C., Schmitz, H. H. and Kelm, M. (2006). (-)-Epicatechin mediates beneficial effects of flavanol-rich cocoa on vascular function in humans. *Proceeding of the National Academy of Sciences of the United States of America*. 103: 1024–1029.

Seeram, N. P., Zhang, Y. and Nair, M. G. (2003). Inhibition of proliferation of human cancer cells and cyclooxygenase enzymes by anthocyanidins and catechins. *Nutrition and Cancer*. 46: 101–106.

Serisier, S., Leray, V., Poudroux, W., Magot, T., Ouguerram, K. And Nguyen, P. (2008). Effects of green tea on insulin sensitivity, lipid profile and expression of PPAR-α and PPAR-γ and their target genes in obese dogs. *British Journal of Nutrition*. 99: 1208–1216.

Shaik, Y. B., Castellani, M. L., Perrella, A., Conti, F., Salini, V., Tete, S., Madhappan, B., Vecchiet, J., De Lutiis, M. A., Caraffa, A. and Cerulli, G. (2006). Role of quercetin (a natural herbal compound) in allergy and inflammation. *Journal of Biological Regulators and Homeostatic Agents*. 20: 47-52.

Shakirin, F. H., Prasad, K. N., Ismail, A., Lau, C. Y. and Azlan, A. (2010). Antioxidant capacity of underutilized Malaysian *Canarium odontophyllum* (dabai) Miq. fruit. *Journal of Food Composition and Analysis.* 23: 777–781.

Shakirin, F. H., Azlan, A., Ismail, A., Amom, Z. and Yuon, L. C. (2012). Antiatherosclerotic effect of *Canarium odontophyllum* Miq. Fruit parts in rabbits fed high cholesterol diet. *Evidence-Based Complementary and Alternative Medicine*. doi:10.1155/2012/838604: 1-10.

Sharma, S. B., Nasir, A., Prabhu, K. M. and Murthy, P.S. (2006). Antihyperglycemic effect of the fruit-pulp of *Eugenia jambolana* in experimental diabetes mellitus. *Journal of Ethnopharmacology.* 104: 367–373.

Shaw, J. E., Sicree, R. A. and Zimmet, P. Z. (2010). Global estimates of the prevalence of diabetes for 2010 and 2030. *Diabetes Research and Clinical Practice*. 87: 4-14.

Singleton, V. L. and Rossi Jr., J. A., (1965). Colorimetry of total phenolics with phosphomolybdic–phosphotungstic acid reagents. *American Journal of Enology and Viticulture.* 16: 144–158.

Somani, R., Sanjay, K. and Singhai, A. K. (2006). Antidiabetic potential of *Butea monosperma* in rats. *Fitoterapia*. 77: 80-90.

Song, J. M., Lee, K. H. and Seong, B. L. (2005). Antiviral effect of catechins in green tea on influenza virus. *Antiviral Research*. 68: 66–74.

Soudami, K. K.; Unnikrishnan, M. C.; Soni, K. B.; Kuttan, R. (1992). Inhibition of lipid peroxidation and cholesterol levels in mice by curcumin. *Indian Journal of Physiology and Pharmacology*. 36; 239–243.

Spira, A., Gowrishankar, M. and Halperin, M. L. (1997). Factors contributing to the degree of polyuria in a patient with poorly controlled diabetes mellitus. *American Journal of Kidney Diseases.* 30; 829–835.

Sri Balasubashini, M., Rukkumani, R. and Menon, V. P. (2003). Protective effects of ferulic acid on hyperlipidemic diabetic rats. *Acta Diabetologica*. 40: 118–122.

Srivinasan, K., Patole, P. S., Kaul, C. L. and Ramarao, P. (2004). Reversal of glucose intolerance by pioglitazone in high-fat diet fed rats. *Methods and Findings in Experimental and Clinical Pharmacology*. 26: 327–33

Srinivasan, K., Viswanad, B., Asrat, L., Kaul, C. L. and Ramarao, P. (2005). Combination of high-fat diet-fed and low-dose stretozotocin-treated rat: A model for type 2 diabetes and pharmacological screening. *Pharmacological Research*. 52: 313–320.

Steinberg, D. (2002). Atherogenesis in perspective: hypercholesterolemia and inflammation as partners in crime. *Nature Medicine*. 8: 1211-1217.

Su, H. C., Hung, L. M. and Chen, J. K. (2006). Resveratrol, a red wine antioxidant, possesses an insulin-like effect in streptozotocin-induced diabetic rats. *American Journal of Physiology - Endocrinology and Metabolism*. 290: E1339–E1346.

Sun, T. and Ho, C. T. (2005). Antioxidant activities of buckwheat extracts. *Food Chemistry*. 90: 743–749.

Sunil, C., Ignacimuthu, S. and Agastian, P. (2011). Antidiabetic effect of *Symplocos cochinchinensis* (Lour.) S. Moore. in type 2 diabetic rats. *Journal of Ethnopharmacology*. 134: 298–304.

Szkudelski, T. (2001). The mechanism of alloxan and streptozotocin action in β-cells of the rat pancreas. *Physiological Research*. 50: 536-546.

Tahraoui, A., El-Hilaly, J., Israili, Z. H. And Lyoussi, B. (2007). Ethnopharmacological survey of plants used in the traditional treatment of hypertension and diabetes in south-eastern Morocco (*Errachidia province*). *Journal of Ethnopharmacology*. 110: 105-117.

Tanaka, T., Masuzaki, H., Ebihara, K., Ogawa, Y., Yasue, S., Yukioka, H., Chusho, H., Miyanaga, F., Miyazawa, T., Fujimoto, M., Kusakabe, T., Kobayashi, N., Hayashi, T., Hosoda, K., and Nakao, K. (2005). Transgenic expression of mutant peroxisome proliferator-activated receptor gamma in liver precipitates fasting-induced steatosis but protects against high-fat diet-induced steatosis in mice. *Metabolism*. 54: 1490–1498.

Tang, C., Han, P., Oprescu, A. I., Lee, S. C., Gyulkhandanyan, A. V., Chan, G. N. Y., Wheeler, M. B. and Giacca, A. (2007). Evidence for role of superoxide generation in glucose-induced β-cell dysfunction In vivo. *Diabetes*. 56: 2722-2731.

Tennvall, G. R. and Apelqvist. J. (2004). Health-economic consequences of diabetic foot lesions. *Clinical Infectious Diseases*. 39: S132–S139.

Thaipong, K., Boonprakob, U., Crosby, K., Cisneros-Zevallos, L. and Byrnec, D. H. (2006). Comparison of ABTS, DPPH, FRAP, and ORAC assays for estimating antioxidant activity from guava fruit extracts. *Journal of Food Composition and Analysis*. 19: 669–675.

The Expert Committee on the diagnosis and classification of diabetes mellitus. (1997). Report of the Expert Committee on the diagnosis and classification of diabetes mellitus. *Diabetes Care*. 20: 1183–1197.

The Expert Committee on the diagnosis and classification of diabetes mellitus. (2003). Follow-up report on the diagnosis of diabetes mellitus. *Diabetes Care*. 26: 3160–3167.

Tiikkainen, M., Hakkinen, A. M., Korsheninnikova, E., Nyman, T., Makimattila, S. and Yki-Jarvinen, H. (2004). Effects of rosiglitazone and metformin on liver fat content, hepatic insulin resistance, insulin clearance, and gene expression in adipose tissue in patients with type 2 diabetes. *Diabetes*. 53: 2169-2176.

Timberlake, C. F. and Henry, B. S. (1986). Plant pigments as natural food colours. *Endeavour*. 10: 31–36.

Tisch, R. and McDevitt, H. (1996). Insulin dependent diabetes mellitus. *Cell*. 85: 291–297.

Tonooka, N., Oseid, E., Zhou, H., Harmon, J. S. and Robertson, R. P. (2007). Glutathione peroxidase protein expression and activity in human islets isolated for transplantation. *Clinical Transplantation*. 21: 767–772.

Udenigwe, C. C., Ramprasath, V. R., Aluko, R. E. and Jones, P. J. H. (2008). Potential of resveratrol in anticancer and anti-inflammatory therapy. *Nutrition Reviews*. 66: 445–454.

UK Prospective Diabetes Study (UKPDS) Group. (1998). Intensive blood glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet. 35;* 837-853.

Utsunomiya, H., Yamakawa, T., Kamei, J., Kadonosono, K. and Tanaka, S. I. (2005). Anti-hyperglycemic effects of plum in rat model of obesity and type-2 diabetes, Wistar fatty rat. *Biomedical Research*. 26: 193-200.

Valcheva-Kuzmanova, S., Kuzmanov, K., Mihova, V., Krasnaliev, I., Borisova, P. and Belcheva, A. (2007). Antihyperlipidemic effect of *Aronia melanocarpa* fruit juice in rats fed a high cholesterol diet. *Plant Food and Human Nutrition*. 62; 19–24.

Valko, M., Leibfritz, D., Moncol, J., Cronin, M. T. D., Mazura, M. and Telserd. (2007). Free radicals and antioxidants in normal physiological functions and human disease. *The International Journal of Biochemistry & Cell Biology*. 39: 44–84.

Vann Epps-Fung, M., Williford, J., Wells, A. and Hardy, R.W. (1997). Fatty acid-induced insulin resistance in adipocytes. *Endocrinology*. 138: 4338-4345.

Velayutham, P., Babu, A. and Liu, D. (2008). Green tea catechins and cardiovascular health: An update. *Current Medicinal Chemistry*. 15: 1840–1850.

Verstraeten, S. V., Keen, C. L., Schmitz, H. H., Fraga, C. G. and Oteiza, P. I. (2003). Flavan-3-ols and procyanidins protect liposomes against lipid oxidation and disruption of the bilayer structure. *Free Radical Biology and Medicine*. 34: 84–92.

Vessal, M., Hemmati, M. and Vaseib, M. (2003). Antidiabetic effects of quercetin in streptozocin-induced diabetic rats. *Comparative Biochemistry and Physiology Part C: Toxicology & Pharmacology*. 135: 357-364.

Villarroya, F., Iglesias, R. and Giralt, M. (2007). PPARs in the control of uncoupling proteins gene expression. *PPAR Research*. 74364: 1-12.

Vincent, A. M., Russell, J. W., Low, P. and Feldman, E. L. (2004). Oxidative stress in the pathogenesis of diabetic neuropathy. *Endocrine Reviews*. 25: 612–628.

Voon, B. H. and Kueh, H. S. (1999). The nutritional value of indigenous fruits and vegetables in Sarawak. *Asia Pacific Journal of Clinical Nutrition*.8: 24–31.

Wautier, J. L. and Guillausseau, P. J. (1998). Diabetes, advanced glycation end products and vascular disease. *Vascular Medicine.* 3: 131-137.

Wautier, J. L. and Guillausseau. (2001). Advanced glycation end products, their receptors and diabetic angiopathy. *Diabetes Metabolism*. 27: 535-542.

Wettasinghe, M. and Sahidi, F. (1999). Antioxidant and free radical-scavenging properties of ethanolic extracts of defatted borage (*Borago officinalis* L.) seeds. *Food Chemistry*. 67; 399-414.

Wild, S., Roglic, G., Green, A., Sicree, R. and King, H. (2004). Global prevalence of diabetes : Estimates for the year 2000 and projections for 2030. *Diabetes Care*. 27: 1047–1053.

WHO, Expert Committee on Diabetes Mellitus. Second Report. Technical Report Series 646, Geneva, World Health Organization, 1980

WHO, Definition, diagnosis and classification of diabetes mellitus and its complications. Geneva, World Health Organization, 1999.

WHO, The world health report 2002-Reducing Risk, promoting healthy life, Geneva, World Health Organization, 2002.

WHO, Global health risks: mortality and burden of disease attributable to selected major risks. Geneva, World Health Organization, 2009.

WHO, Global status report on noncommunicable disease 2010. Geneva, World Health Organization, 2011.

Wolfsdorf, J., Glaser, N. and Sperling, M. A. (2006). Diabetic Ketoacidosis in Infants, Children, and Adolescents; A consensus statement from the American Diabetes Association. *Diabetes Care*. 29: 1150-1159.

Woods, S. C., Seeley, R. J., Rushing, P. A., D'Alessio, D. and Tso, P. (2003). A controlled high-fat diet induces an obese syndrome in rats. *The Journal of Nutrition*. 133: 1081–1087.

Xia, T. and Wang, Q. (2006). Antihyperglycemic effect of *Cucurbita ficifolia* fruit extract in streptozotocin-induced diabetic rats. *Fitoterapia*. 77: 530–533.

Wu, L. Y., Juan, C. C., Ho, L. T., Hsu, Y. P. And Hwang, L. C. (2004). Effect of green tea supplementation on insulin sensitivity in sprague-dawley rats. *Journal of Agricultural and Food Chemistry*. 52: 643-648

Xu, Z., Wang, X., Zhou, M., Ma, L., Deng, Y., Zhang, H., Zhao, A., Zhang, Y. and Jia, W. (2008). The Antidiabetic activity of total lignan from *Fructus arctii* against alloxan-induced diabetes in mice and rats. *Phytotherapy Research*. 22: 97–101.

Wolfram, S., Raederstorff, D., Preller, M., Wang, Y., Teixeira, S. R., Riegger, C. and Weber, P. (2006). Epigallocatechin gallate supplementation alleviates diabetes in rodent. *The Journal of Nutritio*n. 136: 2512–2518.

Yang, J., Campitelli, J., Hu, G., Lin, Y., Luo, J. And Xue, C. (2007). Increase in DPP-IV in the intestine, liver and kidney of the rat treated with high fat diet and streptotzotocin. *Life Sciences*. 81: 272–279.

Yang, T. T. C. and Koo, M. W. L. (2000). Chinese green tea lowers cholesterol level through an increase in fecal lipid excretion. *Life Sciences*. 66: 411-423.

Yao, Y., Li, X. B., Zhao, W., Zeng, Y. Y., Shen, H., Xiang, H. and Xiao, H. (2010). Anti-obesity effect of an isoflavone fatty acid ester on obese mice induced by high fat diet and its potential mechanism. *Lipids in Health and Disease*. 9: 1-12.

Yau, J. W. Y., Rogers, S. L., Kawasaki, R., Lamoureux, E. L., Kowalski, J. W., Bek, T., Chen, S. J., Dekkerm J. M., Fletcher, A., Grauslund, J., Haffner, S., Hamman, R. F., Ikram, M. K., Kayama, T., Klein, B. E. K., Klein, R., Krisnaiah, S., Mayurasakorn, K., O'hare, J., Orchard, T. J., Porta, M., Rema, M., Roy, M. S., Sharma, T., Shaw, J., Taylor, H., Tielsch, J. M., Varma, R., Wang, J. J., Wang, N., West, S., Xu, L., Yasuda, M., Zhang, X., Mitchell, P. and Wong, T. Y. (2012). Global prevalence and major risk factors of diabetic retinopathy. *Diabetes Care*. 35: 556–564.

Yilmazer-Musa, M., Griffith, A. M., Michels, A. J., Schneider, E. and Frei, B. (2012). Grape seed and tea extracts and catechin 3-gallates are potent inhibitors of α-amylase and α-glucosidase activity. *Journal of Agricultural and Food Chemistry*. 60: 8924−8929.

Yki-Järvinen, H. (2004). Thiazolidinediones. *The New England Journal of Medicine*. 351: 1106-1118.

Yoon, M. J., Lee, G. Y., Chung, J. J., Ahn, Y.H., Hong, S. H. and Kim, J. B. (2006). Adiponectin increases fatty acid oxidation in skeletal muscle cells by sequential activation of AMP-activated protein kinase, p38 mitogen-activated protein kinase, and peroxisome proliferator-activated receptor alpha. *Diabetes*. 55: 2562–2570.

Zhang, P., Zhang, X., Brown, J., Vistisen, D., Sicree, R., Shaw, J. and Nichols, G. (2010). Global healthcare expenditure on diabetes for 2010 and 2030. *Diabetes research and clinical practice*. 87: 293–301

Zhang, Z. F., Li, Q., Liang, J., Dai, X. Q. Ding, Y., Wang, J. B. and Li, Y. (2010). Epigallocatechin-3-O-gallate (EGCG) protects the insulin sensitivity in rat L6 muscle cells exposed to dexamethasone condition. *Phytomedicine*. 17: 14–18.

Zhou, J., Zhou, S., Tang, J., Zhang, K., Guang, L., Huang, Y., Xu, Y. And Ying, Y. (2009). Protective effect of berberine on beta cells in streptozotocin- and high-carbohydrate/ high-fat diet-induced diabetic rats. *European Journal of Pharmacology*. 606: 262–268.

Zheng, W. and Wang, S. Y. (2003). Oxygen radical absorbing capacity of phenolics in blueberries, cranberries, chokeberries, and lingonberries. Journal of Agricultural and Food Chemistry. 51; 502−509.

Zorzano, A., Placín and Gumá, A. (2005). Mechanisms regulating GLUT4 glucose transporter expression and glucose transport in skeletal muscle. *Acta Physiologica Scandinavica*. 183: 43–58.

Zunino, S. J., Storms, D. H. and Stephensen, C. B. (2007). Diets rich in polyphenols and vitamin a inhibit the development of type I autoimmune diabetes in nonobese diabetic mice. *The Journal of Nutrition*. 137: 1216–1221.