THE EFFECT OF ANTIDIABETIC ACTIVITY OF *EURYCOMA LONGIFOLIA*, *ORTHOSIPHON STAMINEUS* AND *PUNICA GRANATUM* COMBINED EXTRACTS ON STREPTOZOTOCIN-INDUCED DIABETIC RATS

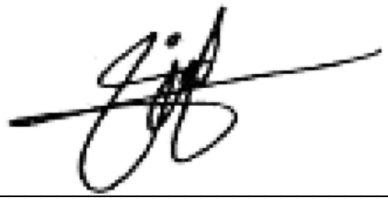
OSAMA ABDULMUNEM KHAYRI AL-OBAIDI

DOCTOR OF PHILOSOPHY

UNIVERSITI MALAYSIA PAHANG

SUPERVISOR'S DECLARATION

We hereby declare that We have checked this thesis/project and in our opinion, this thesis is adequate in terms of scope and quality for the award of the Doctor of Philosophy.



(Supervisor's Signature)

Full Name : DR. ESSAM A. MAKKY

Position : ASSOC. PROF.

Date : 16 FEBRUARY 2020

DR. ESSAM A. MAKKY
Associate Professor
Faculty of Industrial Sciences & Technology
Universiti Malaysia Pahang
Lebuhraya Tun Razak, 26300 Gambang,
Kuantan, Pahang.
Tel +609-5492454 Fax +609-5492766
Email essam22001@gmail.com
essammakky@ump.edu.my

(Co-supervisor's Signature)

Full Name : DR. NORMAZA BINTI ZAMRI

Position : SENIOR LECTURER

Date : 16 FEBRUARY 2020

DR.NORMAIZA BINTI ZAMRI
Pensyarah Kanan
Fakulti Sains & Teknologi Industri UMP
Lebuhraya Tun Razak, 26300 Gambang,
Kuantan, Pahang
Tel 09-549 2302 Fax 09-549 2766
Email: maiza@ump.edu.my

STUDENT'S DECLARATION

I hereby declare that the work in this thesis is based on my original work except for quotations and citations which have been duly acknowledged. I also declare that it has not been previously or concurrently submitted for any other degree at Universiti Malaysia Pahang or any other institutions.

_____

(Student's Signature)

Full Name : OSAMA ABDULMUNEM KHAYRI AL-OBAIDI

ID Number : PKT15004

Date : 16 FEBRUARY 2020

THE EFFECT OF ANTIDIABETIC ACTIVITY OF *EURYCOMA LONGIFOLIA*, *ORTHOSIPHON STAMINEUS* AND *PUNICA GRANATUM* COMBINED EXTRACTS ON STREPTOZOTOCIN-INDUCED DIABETIC RATS

OSAMA ABDULMUNEM KHAYRI AL-OBAIDI

Thesis submitted in fulfillment of the requirements
for the award of the degree of
Doctor of Philosophy in Industrial Biotechnology

Faculty of Industrial Sciences and Technology

UNIVERSITI MALAYSIA PAHANG

FEBRUARY 2021

ACKNOWLEDGEMENTS

So many to thank, so few pages…Thanks be to Allah, for life and a measure of health and mental fortitude to finally.

I owe my deepest gratitude to my supervisor professor, Assoc. Prof. Dr. Essam Abdellatif Makky Saleh. without his enthusiasm, encouragement, support and continuous optimism this thesis would hardly have been completed.

I would like to thank my co-supervisor, Dr. Normaza Binti Zamri for her support at the beginning of this project, for the use of their facilities in the laboratory and for her detailed and constructive comments and organized working style throughout the project.

I am forever thankful to my colleagues at the Faculty of Industrial Sciences and Technology, Universiti Malaysia Pahang for their friendship and support, and for creating a cordial working environment. I thankfully acknowledge the contributions of Science Officers of FIST laboratory.

Most importantly, I would like to thank my mom, dad, for all their love, support and for always believing in me and never giving up on me, even when I dint believe in myself. I cannot finish without saying how grateful I am to all my parents, who supported me emotionally and financially. I always knew that you believed in me and wanted the best for me. Thank you for teaching me that my job in life was to learn, to be happy, and to know and understand myself; only then could I know and understand others, especially my dad who dedicated his lives to education and taught me to be respectful and thankful for education. This study is a result of a love of learning and a desire to help others that I learned from dad.

To my sisters, thanks for always being positive and for reminding me of where I've come from, where I'm going and why this matters.

To my brothers, thanks for blindly throwing your means behind me so I could focus on finishing. I have no idea why you kept on believing that I could do it, but I'm surely glad you did.

ABSTRAK

Diabetes mellitus (DM) adalah sindrom metabolik yang kini dikendalikan menggunakan pelbagai jenis ubat yang ditetapkan; namun, ubat-ubatan ini dikaitkan dengan kesan sampingan yang berbeza. Oleh itu, tanaman perubatan dianggap sebagai alternatif dalam perubatan tradisional untuk merawat DM kerana mereka tidak mempunyai kesan sampingan. Kajian ini dibuat dengan tujuan untuk mengkaji amnya ekstrak tumbuhan perubatan dari segi aktiviti perencatan enzim α-amylase dan α-glucosidase; untuk mengkaji kesan pelindung buah pinggang, hepatik, dan pankreas *ElE:OsC* (2:1) dan *ElE:PgC* (2:1) ekstrak tumbuhan pada tikus diabetes yang disebabkan oleh streptozotocin (STZ) selepas 30 hari rawatan. Tikus Sprague-Dawley disuntik secara intraperitoneal dengan STZ (60 mg/kg) untuk mendorong DM. Tikus dikelompokkan secara rawak ke dalam 7 kumpulan 5 tikus masing-masing berdasarkan rawatan yang dimaksudkan untuk kumpulan tersebut; tujuh kumpulan tikus adalah seperti berikut: NC = tikus kawalan normal; N*ElE:PgC* (2:1) = tikus normal yang dirawat dengan ekstrak *E. longifolia* dan *P. granatum* gabungan pada nisbah gabungan 2:1 (200 mg / kg); N*ElE:OsC* (2:1) = tikus normal yang dirawat dengan ekstrak gabungan *E. longifolia* dan *O. stamineus* pada nisbah gabungan 2:1; DC = tikus kawalan diabetes; DG = tikus diabetes yang dirawat glibenclamide (0.6 mg / kg); D*ElE:PgC* (2:1) = tikus diabetes yang dirawat dengan ekstrak gabungan *E. longifolia* dan *P. granatum* pada nisbah 2:1 (200 mg / kg); D*ElE:OsC* (2:1) = tikus diabetes yang dirawat dengan ekstrak gabungan *E. longifolia* dan *O. stamineus* pada nisbah yang sama. Semua kumpulan haiwan dirawat selama 4 minggu dan setelah tempoh rawatan, tahap glukosa darah, berat badan, fungsi hati dan ginjal, dan perubahan histopatologi pankreas endokrin, hati dan ginjal diperiksa pada semua tikus eksperimen. Ekstrak dengan aktiviti perencatan enzim $\geq$ 50% dilaporkan dalam *A. bilimbi*, *A. paniculata*, *O. stamineus*, *E. longifolia* dan *P. granatum*. Hasil kajian menunjukkan bahawa gabungan 2:1 ekstrak etanolik *E. longifolia* dan ekstrak kloroform *P. granatum* menunjukkan kadar perencatan maksimum α-glucosidase (148.06%), sementara kombinasi sama ekstrak etanol *E. longifolia* dan kloroform *O. stamineus* menawarkan perencatan α-glucosidase terhebat (137.43%). Analisis fitokimia berasaskan ekstrak GC-MS menunjukkan adanya asid lemak dalam ekstrak-ekstrak tersebut, dengan asid palmitik, merupakan asid lemak yang paling tinggi berlaku dalam ekstrak *O. stamineus*. Pemerhatian biokimia menunjukkan peningkatan yang signifikan ($p<0.05$) pada tahap glukosa darah puasa, berat hati relatif, tahap AST, ALT, GGT dan ALP, tahap urea darah dan tahap kreatinin serum dalam kumpulan DC berbanding dengan kumpulan NC. Walau bagaimanapun, perubahan dalam parameter ini ditingkatkan dalam kumpulan D*ElE:OsC* (2:1), D*ElE:PgC* (2:1) dan DG; kesan penambahbaikan adalah signifikan dalam kumpulan DG dan D*ElE:PgC* (2:1) sahaja ($p<0.05$). Pemeriksaan hati/hepatik menunjukkan vakuolasi ringan pada sitoplasma hepatosit, kesesakan pada vena tengah, vena portal dan sinusoid, serta kecelaruan ringan kord hepatic, pada kumpulan DC. Perubahan patologi ini diperbaiki dalam tikus yang dirawat *ElE:OsC* (2:1), *ElE:PgC* (2:1) dan glibenclamide. Pemerhatian histologi pankreas tikus dalam kumpulan DC menunjukkan sejumlah kecil, pulau kecil Langerhans yang tersebar di dalam acini. Sel-sel pulau mempunyai nukleus piknotik dan sitoplasma eosinofilik yang sedikit. Fibrosis dilihat dalam beberapa kawasan, sementara bahagian ginjal menunjukkan struktur histologi normal (glomeruli, tubulus ginjal, saluran darah dan interstitium) ginjal dengan NC, DM, dan tikus yang dirawat. Sebagai kesimpulan, hasil kajian ini menunjukkan bahawa ekstrak *ElE:OsC* (2:1) dan *ElE:PgC* (2:1) ekstrak tumbuhan dapat berfungsi sebagai alternatif yang berpotensi untuk rawatan dan kawalan diabetes mellitus dan komplikasi yang berkaitan pada tikus diabetes mellitus.

ABSTRACT

Diabetes mellitus (DM) is a metabolic syndrome that is currently being managed using different brands of prescribed medications; however, these medications are associated with different side effects. As such, medical plants are considered an alternative in traditional medicines for treating DM as they have no side effects. The present study was conceived with the aim of studying generally medicinal plants extracts in terms of their α-amylase and α-glucosidase inhibitory activities; to study the renal, hepatic, and pancreatic protective effects of these *ElE:OsC* (2:1) and *ElE:PgC* (2:1) plant extracts on streptozotocin (STZ)-induced diabetic rats after 30 days of treatment. Sprague-Dawley rats were intraperitoneally injected with STZ (60 mg/kg) to induce DM. The rats were randomly grouped into 7 groups of 5 rats each based on the intended treatment for the groups; the seven groups of rats are as follows: NC = normal control rats; N*ElE:PgC* (2:1) = normal rats treated with combined *E. longifolia* and *P. granatum* extracts at a combination ratio of 2:1 (200 mg/kg); N*ElE:OsC* (2:1) = normal rats treated with combined extracts of *E. longifolia* and *O. stamineus* at 2:1 combination ratio; DC = diabetic control rats; DG = glibenclamide (0.6 mg/kg)-treated diabetic rats; D*ElE:PgC* (2:1) = diabetic rats treated with combined extracts of *E. longifolia* and *P. granatum* at a ratio of 2:1 (200 mg/kg); D*ElE:OsC* (2:1) = diabetic rats treated with combined extracts of *E. longifolia* and *O. stamineus* at the same ratio. All the animal groups were treated for 4 weeks and after the treatment period, the blood glucose level, body weight, liver and renal functions, and histopathological changes of the endocrine pancreas, liver and kidneys were examined in all the experimental rats. The extracts with ≥ 50% enzyme inhibition activity were reported in *A. bilimbi*, *A. paniculata*, *O. stamineus*, *E. longifolia* and *P. granatum*. The outcome of the study showed that a 2:1 combination of ethanolic extract of *E. longifolia* and chloroform extract of *P. granatum* showed gave the maximum rate of α-glucosidase inhibition (148.06%), while a similar combination of ethanol extract of *E. longifolia* and chloroform extract of *O. stamineus* offered the greatest α-glucosidase inhibition (137.43%). GC-MS-based phytochemical analysis of the extracts showed the presence of fatty acids in the extracts, with palmitic acid being the highest occurring fatty acid in the extracts of *O. stamineus*. Results showed a significantly increase ($p<0.05$) in fasting blood glucose level, body weight, AST, ALT, ALP and GGT levels, total protein, albumin, globulin, blood urea level and serum creatinine level in the DC group compared to the NC group. However, changes in these parameters were ameliorated in the D*ElE:OsC* (2:1), D*ElE:PgC* (2:1) and DG groups; the ameliorative effect was significant in the DG and D*ElE:PgC* (2:1) groups only ($p<0.05$). Examination of the liver sections showed mild vacuolation in the cytoplasm of the hepatocytes, congestion in the central vein, portal vein and sinusoid, as well as mild hepatic cord disarrangement in the DC group. These pathological changes were ameliorated in the *ElE:OsC* (2:1), *ElE:PgC* (2:1) and glibenclamide-treated rats. Histological observation of the pancreas sections of the rats in the DC group showed scanty number of small sized islets of Langerhans which were scattered within the acini. The islets cells have pyknotic nuclei and scanty eosinophilic cytoplasm. Fibrosis was noted in some areas while sections of the kidneys showed normal histological structure (glomeruli, renal tubules, blood vessels and interstitium) of the kidneys the NC, DM, and treated rats. In conclusion, the outcome of this study showed that *ElE:OsC* (2:1) and *ElE:PgC* (2:1) plant extracts could serve as potential alternatives for the treatment and control of diabetes mellitus and its related complications in diabetes mellitus rats.

TABLE OF CONTENT

LIST OF TABLES

LIST OF FIGURES

LIST OF SYMBOLS

°C	Degree Celsius
W	Watt
H	Hour
Min	Minute
µl	Microliter
M	Molarity
PH	Power of hydrogen
Mg	Megagram
Dw	Distilled water
Ml	Millilitre
Nm	Nanometer
SD	Standard deviation
U/ml	Units per millilitre
mM	Millimolar
µg/kg	Microgramme per kilogramme
Mmol/l	Millimoles per litre
µmol/l	Micromole per litre

LIST OF ABBREVIATIONS

Ab	*Averrhoa bilimbi*
ADH	Anti-diuretic hormone
AF	Aqueous fraction
AFR	Africa
AGLs	α-glucosidase inhibitors
AKt	Protein kinase A
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AMPK	5' adenosine monophosphate-activated protein kinase
ANOVA	Analysis of Variance
Ap	*Andrographis paniculata*
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
AVP	Arginine vasopressin
BW	Body weight
CKD	Chronic kidney diseases
CMC	Carboxymethyl cellulose
CV	Central vein
CVD	Cardiovascular diseases
DC	Diabetic control
DI	Diabetes insipidus
DM	Diabetes mellitus
DNL	De novo lipogenesis
DNS	3,5-Dinitrosalicylic acid
DPPIV	Dipeptidyl peptidase IV
DPX	Dibutylphthalate Polystyrene Xylene
DW	Distilled water
El	*Eurycoma longifolia*
ElE	Ethanolic *E. longifolia* extract
EUR	Europe
FA/FA	Zucker Diabetic Fatty

FAO	Food and Agriculture Organization
FBG	Fasting blood glucose
FC	Fatty degeneration
FFAs	Free fatty acids
FIST	Faculty of Industrial Sciences & Technology
GC-MS	Gas chromatography–mass spectrometry
GDM	Gestational diabetes mellitus
GGT	Gamma-glutamyl transferase
GIP	Glucose-dependent insulinotropic polyopeptide
GLP-1	Glucagon-like peptide 1
GP	Gynura procumbens
GSH	Glutathione
H	Hepatocytes
H&E	Haematoxylin and eosins
HDL	High-density lipoprotein
HFD	High fat diet
I.V.	Intravenous
IDF	International Diabetes Federation
IGT	impaired glucose tolerance
IR	Insulin receptors
KATP	ATP-sensitive potassium channel
KH	Kelulut honey
LDL	Low-density lipoprotein
MENA	Middle east and north Africa
NAC	North America and Caribbean
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
NC	Normal control
Os	*Orthosiphon stamineu*
OsC	Chloroform extract of *orthosiphon stamineu*
PA	Pancreatic acini
PDN	Painful diabetic neuropathy
Pg	*Punica granatum*

PgC	Chloroform extract of *punica granatum*
PI3K	phosphatidylinositol 3-kinase
PIP2	Phosphatidylinositol (3,4)-bisphosphate
PIP3	Phosphatidylinositol (3,4,5)-trisphosphate
pNPG	p-nitrophenyl glucopyranoside
PP	Pomegranate peel
PPARs	Peroxisome proliferator-activated receptor
PPE	Personal protective equipment
ROS	Reactive oxygen species
S	Sinusoids
SACA	South and Central America
SEA	South-East Asia
Sm	*Swietenia macrophylla*
STZ	Streptozotocin
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TAG	Triacylglyceride
TG	Triglyceride
TNF	Tumor necrosis factor
TZD	Thiazolidinediones
VC	Cytoplasmic vacuolation
VLDL	Very low density lipoprotein
WP	Western Pacific
ZDF	Obese Zucker Rat

REFERENCES

Abbott, C. A., Malik, R. A., van Ross, E. R., Kulkarni, J., & Boulton, A. J. (2011). Prevalence and characteristics of painful diabetic neuropathy in a large community-based diabetic population in the UK. *Diabetes care*, *34*(10), 2220-2224.

Abdullah, M., G. K. Dash and S. Acharyya (2013). Antihyperglycemic and antilipidemic activity of Anthocephalus cadamba (roxb.) Miq. roots."

Abeeleh, M. A., Ismail, Z. B., Alzaben, K. R., Abu-Halaweh, S. A., Al-Essa, M. K., Abuabeeleh, J., & Alsmady, M. M. (2009). Induction of diabetes mellitus in rats using intraperitoneal streptozotocin: a comparison between 2 strains of rats. *Eur J Sci Res*, *32*(3), 398-402.

Adaramoye, O. A. (2012). Antidiabetic effect of kolaviron, a biflavonoid complex isolated from Garcinia kola seeds, in Wistar rats. *African Health Sciences*, *12*(4), 498-506.

Adeyemi, D. O., Ukwenya, V. O., Obuotor, E. M., & Adewole, S. O. (2014). Anti-hepatotoxic activities of Hibiscus sabdariffa L. in animal model of streptozotocin diabetes-induced liver damage. *BMC complementary and alternative medicine*, *14*(1), 277.

Ahad, H. A., Kumar, C. S., Nanda, P. S. M., Bhanu, T. U., Ravindra, B. V., & Mohan, G. V. (2010). Traditional indian herbs used for diabetes. *Hindustan Abdul Ahad et al/JITPS*, *1*(2), 69-78.

Ahmed, A. T., Belal, S. K., & Salem, A. G. E. (2014). Protective effect of pomegranate peel extract against diabetic-induced renal histopathological changes in albino rats. *IOSR-JDMS*, *13*(10), 94-105.

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

Akilandeswari, G., Anand, A. V., Sampathkumar, P., Moorthi, P. V., & Preethi, B. (2019). A Prospective Review on Phyto-Pharmacological Aspects of Andrographis paniculata. *Systematic Reviews in Pharmacy*, *10*(1), 15-19.

Akmar, K., & Noor, M. M. (2019). Effect of combination of Gynura procumbens aqueous extract and Trigona spp. honey on fertility and libido of streptozotocin-induced hyperglycaemic male rats. *Asian Pacific Journal of Reproduction*, *8*(2), 56.

Alam, S., S. K. Reddy, A. Baig, M. K. Reddy, M. Mohiuddin, M. V. Reddy and R. K. Gupta (2013). "Evaluation of antidiabetic and anti-lipidimic potential of kalongi sugar powder water extract in stz induced diabetic rats. *Int J Pharm Pharm Sci*, *5*(1), 94-96.

Al-Ani, F. S. (2009). Accreditation. *Iraqi Journal of Medical Sciences 7*(4): 1-3.

Al-Azzawie, H. F. and M.S. S. Alhamdani (2006). Hypoglycemic and antioxidant effect of oleuropein in alloxan-diabetic rabbits. *Life sciences 78*(12): 1371-1377.

Alberti, K. G. M. M., P. Zimmet and J. Shaw (2007). International Diabetes Federation: a consensus on Type 2 diabetes prevention. *Diabetic Medicine 24*(5): 451-463.

Ali, H., Houghton, P. J., & Soumyanath, A. (2006). α-Amylase inhibitory activity of some Malaysian plants used to treat diabetes; with particular reference to Phyllanthus amarus. *Journal of ethnopharmacology*, *107*(3), 449-455.

Al-Masri, I. M., M. K. Mohammad and M. O. Tahaa (2009). Inhibition of dipeptidyl peptidase IV (DPP IV) is one of the mechanisms explaining the hypoglycemic effect of berberine. *Journal of enzyme inhibition and medicinal chemistry 24*(5): 1061-1066.

Alshawsh, M. A., M. A. Abdulla, S. Ismail and Z. A. Amin (2011). Hepatoprotective effects of Orthosiphon stamineus extract on thioacetamide-induced liver cirrhosis in rats. *Evidence-based complementary and alternative medicine 2011*.

Althunibat, O. Y., A. H. Al-Mustafa, K. Tarawneh, K. M. Khleifat, B. Ridzwan and H. N. Qaralleh (2010). Protective role of Punica granatum L. peel extract against oxidative damage in experimental diabetic rats. *Process Biochemistry 45*(4): 581-585.

Al-Zoreky, N. (2009). Antimicrobial activity of pomegranate (Punica granatum L.) fruit peels. *International journal of food microbiology 134*(3): 244-248.

Ameer, O. Z., I. M. Salman, M. Z. Asmawi, Z. O. Ibraheem and M. F. Yam (2012). Orthosiphon stamineus: traditional uses, phytochemistry, pharmacology, and toxicology. *Journal of medicinal food 15*(8): 678-690.

American Diabetes Association. (2020). 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2020. *Diabetes Care, 43*(Supplement 1), S14-S31.

Anthony, P., K. Ishak, N. Nayak, H. Poulsen, P. Scheuer and L. Sobin (1977). The morphology of cirrhosis: definition, nomenclature, and classification. *Bulletin of the World Health Organization 55*(4): 521.

Aruoma, O. I., V. S. Neergheen, T. Bahorun and L.S. Jen (2006). Free radicals, antioxidants and diabetes: embryopathy, retinopathy, neuropathy, nephropathy and cardiovascular complications. *Neuroembryology and Aging 4*(3): 117-137.

Aslam, A., Singh, J., & Rajbhandari, S. (2014). Pathogenesis of painful diabetic neuropathy. *Pain research and treatment, 2014*.

Atlas, D. (2015). International diabetes federation. IDF Diabetes Atlas, 7th edn. Brussels, Belgium: *International Diabetes Federation.*

Atlas, I. D. (2017). In., 6th edn. Brussels, Belgium: International Diabetes Federation; 2013. *International Diabetes Federation*.

Aviram, M. and L. Dornfeld (2001). Pomegranate juice consumption inhibits serum angiotensin converting enzyme activity and reduces systolic blood pressure. *Atherosclerosis 158*(1): 195-198.

Babey, M., P. Kopp and G. L. Robertson (2011). Familial forms of diabetes insipidus: clinical and molecular characteristics. *Nature Reviews Endocrinology 7*(12): 701.

Bailey, C. J., & Day, C. (2002). Future therapies. *Current medical research and opinion*, *18*(sup1), s82-s88.

Bakatselos, S. O. (2011). Hypoglycemia unawareness. *Diabetes research and clinical practice*, *93*, S92-S96.

Bakeri, N. A., Mohamed Zahari, M. A., Kamarulzaman, F., Yusof, N., Mustafa, N. M., Md Salleh, L., & Md Norodin, N. S. (2018). Inhibitory Effects of Swietenia Mahagoni Seeds Extract on A-Glucosidase and A-Amylase. *International Journal of Engineering*, *31*(8), 1308-1317.

Banihani, S., S. Swedan and Z. Alguraan (2013). Pomegranate and type 2 diabetes. *Nutrition research 33*(5): 341-348.

Barathikannan, K., Venkatadri, B., Khusro, A., Al-Dhabi, N. A., Agastian, P., Arasu, M. V., & Kim, Y. O. (2016). Chemical analysis of Punica granatum fruit peel and its in vitro and in vivo biological properties. *BMC complementary and alternative medicine*, *16*(1), 264.

Bell Jr, R. H. and R. J. Hye (1983). Animal models of diabetes mellitus: physiology and pathology. *Journal of surgical Research 35*(5): 433-460.

Bellamy, L., J.-P. Casas, A. D. Hingorani and D. Williams (2009). Type 2 diabetes mellitus after gestational diabetes: a systematic review and meta-analysis. *The Lancet 373*(9677): 1773-1779.

Bellentani, S., F. Scaglioni, M. Marino and G. Bedogni (2010). Epidemiology of non-alcoholic fatty liver disease. *Digestive diseases 28*(1): 155-161.

Benninger, R. K., W. S. Head, M. Zhang, L. S. Satin and D. W. Piston (2011). Gap junctions and other mechanisms of cell–cell communication regulate basal insulin secretion in the pancreatic islet. *The Journal of physiology 589*(22): 5453-5466.

Bhandari, P. R. (2012). "Pomegranate (Punica granatum L). Ancient seeds for modern cure? Review of potential therapeutic applications. *International Journal of Nutrition, Pharmacology, Neurological Diseases 2*(3): 171.

Bhat, R. and A. Karim (2010). Tongkat Ali (Eurycoma longifolia Jack): a review on its ethnobotany and pharmacological importance. *Fitoterapia 81*(7): 669-679.

Bruce, M. P., & Mallika, M. C. V. (2019). Prevalence of complications of diabetes among patients with diabetes mellitus attending a tertiary care centre in Tamil Nadu. *International Journal of Community Medicine and Public Health*, *6*(4), 1452-6.

Brunton, S. (2009). Beyond glycemic control: treating the entire type 2 diabetes disorder. *Postgraduate medicine 121*(5): 68-81.

Buchanan, T. A. and A. H. Xiang (2005). Gestational diabetes mellitus. *The Journal of clinical investigation 115*(3): 485-491.

Bugianesi, E., A. Gastaldelli, E. Vanni, R. Gambino, M. Cassader, S. Baldi, V. Ponti, G. Pagano, E. Ferrannini and M. Rizzetto (2005). Insulin resistance in non-diabetic patients with non-alcoholic fatty liver disease: sites and mechanisms. *Diabetologia 48*(4): 634-642.

Butler, A. E., J. Janson, S. Bonner-Weir, R. Ritzel, R. A. Rizza and P. C. Butler (2003). β-cell deficit and increased β-cell apoptosis in humans with type 2 diabetes. *Diabetes 52*(1): 102-110.

Calabrese, A., D. Caton and P. Meda (2004). Differentiating the effects of Cx36 and E-cadherin for proper insulin secretion of MIN6 cells. *Experimental cell research 294*(2): 379-391.

Çam, M., & İçyer, N. C. (2015). Phenolics of pomegranate peels: extraction optimization by central composite design and alpha glucosidase inhibition potentials. *Journal of food science and technology, 52*(3), 1489-1497.

Cardiff, R. D., Miller, C. H., & Munn, R. J. (2014). Manual hematoxylin and eosin staining of mouse tissue sections. *Cold Spring Harbor Protocols, 2014*(6), pdb-prot073411.

Caspary, W. F. (1992). Physiology and pathophysiology of intestinal absorption. *The American Journal of Clinical Nutrition*, 299S-308S.

Cefalu, W. T. (2006). Animal models of type 2 diabetes: clinical presentation and pathophysiological relevance to the human condition. *ILAR journal 47*(3): 186-198.

Ceriello, A., Taboga, C., Tonutti, L., Giacomello, R., Stel, L., Motz, E., & Pirisi, M. (1996). Post-meal coagulation activation in diabetes mellitus: the effect of acarbose. *Diabetologia, 39*(4), 469-473.

Kam, A., Li, K. M., Razmovski-Naumovski, V., Nammi, S., Shi, J., Chan, K., & Li, G. Q. (2013). A Comparative Study on the Inhibitory Effects of Different Parts and Chemical Constituents of Pomegranate on α-Amylase and α-Glucosidase. *Phytotherapy Research, 27*(11), 1614-1620.

Chang, C.-M., C.-J. Hsieh, J.-C. Huang and I.-C. Huang (2012). Acute and chronic fluctuations in blood glucose levels can increase oxidative stress in type 2 diabetes mellitus. *Acta diabetologica 49*(1): 171-177.

Charpentier, G., Riveline, J. P., & Varroud-Vial, M. (2000). Management of drugs affecting blood glucose in diabetic patients with renal failure. *Diabetes & metabolism*, *26*, 73-85.

Chatzigeorgiou, A., A. Halapas, K. Kalafatakis and E. Kamper (2009). The use of animal models in the study of diabetes mellitus. *In Vivo 23*(2): 245-258.

Cheah, Y. K., M. Azahadi, S. N. Phang and N. H. A. Manaf (2019). Vigorous and moderate physical activity among overweight and obese adults in Malaysia: Sociodemographic correlates. *Obesity Medicine 15*: 100114.

Cheng, A. and C. D. A. C. P. G. E. Committee (2013). Canadian Diabetes Association 2013 clinical practice guidelines for the prevention and management of diabetes in Canada. Introduction. *Canadian journal of diabetes 37*: S1.

Chiba, S. (1997). Molecular mechanism in α-glucosidase and glucoamylase. *Bioscience, biotechnology, and biochemistry*, *61*(8), 1233-1239.

Chukwuma, C. I., Mashele, S. S., & Akuru, E. A. (2020). Evaluation of the in vitroα-amylase inhibitory, antiglycation, and antioxidant properties of Punica granatum L.(pomegranate) fruit peel acetone extract and its effect on glucose uptake and oxidative stress in hepatocytes. *Journal of Food Biochemistry*, e13175.

Centers for Disease Control and Prevention. (2011). National diabetes fact sheet: national estimates and general information on diabetes and prediabetes in the United States, 2011. *Atlanta, GA: US department of health and human services, centers for disease control and prevention*, *201*(1), 2568-2569.

Centers for Disease Control and Prevention. (2014). National diabetes statistics report: estimates of diabetes and its burden in the United States, 2014. *Atlanta, GA: US Department of Health and Human Services, 2014*.

Control, C. f. D. and Prevention (2017). National diabetes statistics report, 2017. *Atlanta, GA: Centers for Disease Control and Prevention, US Department of Health and Human Services* 20.

Dallas, J. (2011). Diabetes, Doctors and Dogs: An exhibition on Diabetes and Endocrinology by the College Library for the 43rd St. In *Andrew's Day Festival Symposium*.

Daneman, D. (2006). Type 1 diabetes. *The Lancet 367*(9513): 847-858.

Deeds, M., J. Anderson, A. Armstrong, D. Gastineau, H. Hiddinga, A. Jahangir, N. Eberhardt and Y. C. Kudva (2011). Single dose streptozotocin-induced diabetes: considerations for study design in islet transplantation models. *Laboratory animals 45*(3): 131-140.

Devendra, D., E. Liu and G. S. Eisenbarth (2004). Type 1 diabetes: recent developments. *BMJ: British Medical Journal 328*(7442): 750.

Dokken, B. B. (2008). The pathophysiology of cardiovascular disease and diabetes: beyond blood pressure and lipids. *Diabetes Spectrum 21*(3): 160-165.

Duby, J. J., R. K. Campbell, S. M. Setter and K. Rasmussen (2004). Diabetic neuropathy: an intensive review. *American Journal of Health-System Pharmacy 61*(2): 160-173.

Dyachok, O., Isakov, Y., Sågetorp, J., & Tengholm, A. (2006). Oscillations of cyclic AMP in hormone-stimulated insulin-secreting β-cells. *Nature*, *439*(7074), 349-352.

Satyavati, G. V., Raina, M. K., & Sharma, M. (1976). Medicinal Plants of India, vol. I, IndianCouncilof Med. *Res., New Delhi, India*, 201-206.

Eggen, T. and C. Lillo (2012). Antidiabetic II drug metformin in plants: uptake and translocation to edible parts of cereals, oily seeds, beans, tomato, squash, carrots, and potatoes. *Journal of agricultural and food chemistry 60*(28): 6929-6935.

El Deeb, K. S., H. H. Eid, Z. Y. Ali, M. M. Shams and A. M. Elfiky (2019). Bioassay-guided fractionation and identification of antidiabetic compounds from the rind of Punica Granatum Var. nana. *Natural product research*: 1-4.

Eleazu, C. O., K. C. Eleazu, S. Chukwuma and U. N. Essien (2013). Review of the mechanism of cell death resulting from streptozotocin challenge in experimental animals, its practical use and potential risk to humans. *Journal of Diabetes & Metabolic Disorders 12*(1): 60.

Eliakim-Ikechukwu, C. and A. Obri (2009). Histological changes in the pancreas following administration of ethanolic extract of Alchornea cordifolia leaf in alloxan-induced diabetic wistar rats. *Nigerian Journal of Physiological Sciences 24*(2).

Elias, C. F., C. Aschkenasi, C. Lee, J. Kelly, R. S. Ahima, C. Bjorbæk, J. S. Flier, C. B. Saper and J. K. Elmquist (1999). Leptin differentially regulates NPY and POMC neurons projecting to the lateral hypothalamic area. *Neuron 23*(4): 775-786.

Eliza, J., P. Daisy, S. Ignacimuthu and V. Duraipandiyan (2009). Antidiabetic and antilipidemic effect of eremanthin from Costus speciosus (Koen.) Sm., in STZ-induced diabetic rats. *Chemico-biological interactions 182*(1): 67-72.

Elkayal, A. H., Hefny, A. M., Mahmoud, B. A., & Anany, A. M. A. (2020). Health Effects of Abdominal Liposuction in Newly Diagnosed Type 2 Diabetes. *QJM: An International Journal of Medicine, 113*(Supplement_1), hcaa050-056.

Elsner, M., B. Guldbakke, M. Tiedge, R. Munday and S. Lenzen (2000). Relative importance of transport and alkylation for pancreatic beta-cell toxicity of streptozotocin. *Diabetologia 43*(12): 1528-1533.

Elsner, M., E. Gurgul-Convey and S. Lenzen (2008). Relation between triketone structure, generation of reactive oxygen species, and selective toxicity of the diabetogenic agent alloxan. *Antioxidants & redox signaling 10*(4): 691-700.

Erejuwa, O. O., Sulaiman, S. A., Wahab, M. S., Sirajudeen, K. N. S., Salleh, M. S. M., & Gurtu, S. (2011). Effect of glibenclamide alone versus glibenclamide and honey on oxidative stress in pancreas of streptozotocin-induced diabetic rats. *International Journal of Applied Research in Natural Products*, *4*(2), 1-10.

Farswan, M., P. M. Mazumder and V. Percha (2009). Protective effect of Cassia glauca Linn. on the serum glucose and hepatic enzymes level in streptozotocin induced NIDDM in rats. *Indian journal of pharmacology 41*(1): 19.

Fawole, O. A., N. P. Makunga and U. L. Opara (2012). Antibacterial, antioxidant and tyrosinase-inhibition activities of pomegranate fruit peel methanolic extract. *BMC complementary and alternative medicine 12*(1): 200.

Feldman, A. T., & Wolfe, D. (2014). Tissue processing and hematoxylin and eosin staining. In *Histopathology* (pp. 31-43). Humana Press, New York, NY.

Ferrara, A. (2007). Increasing prevalence of gestational diabetes mellitus: a public health perspective. *Diabetes care 30*(Supplement 2): S141-S146.

Fischer, U. A., R. Carle and D. R. Kammerer (2011). Identification and quantification of phenolic compounds from pomegranate (Punica granatum L.) peel, mesocarp, aril and differently produced juices by HPLC-DAD–ESI/MSn. *Food chemistry 127*(2): 807-821.

Flier, J. S. (2019). Starvation in the Midst of Plenty: Reflections on the History and Biology of Insulin and Leptin. *Endocrine reviews*, *40*(1), 1-16.

Friedman, J. M., R. Leibel, D. Siegel, J. Walsh and N. Bahary (1991). Molecular mapping of the mouse ob mutation. *Genomics 11*(4): 1054-1062.

Gabbay, R. A., I. Lendel, T. M. Saleem, G. Shaeffer, A. M. Adelman, D. T. Mauger, M. Collins and R. C. Polomano (2006). Nurse case management improves blood pressure, emotional distress and diabetes complication screening. *Diabetes research and clinical practice 71*(1): 28-35.

Gage, G. J., Kipke, D. R., & Shain, W. (2012). Whole animal perfusion fixation for rodents. *JoVE (Journal of Visualized Experiments)*, (65), e3564.

Gajdosik, A., A. Gajdosikova, M. Stefek, J. Navarova and R. Hozova (1999). Streptozotocin-induced experimental diabetes in male Wistar rats. *General physiology and biophysics 18*: 54-62.

Genco, R. J., Graziani, F., & Hasturk, H. (2020). Effects of periodontal disease on glycemic control, complications, and incidence of diabetes mellitus. *Periodontology 2000*, 83(1), 59-65.

Gharti K. P., Chidi B. B., Bharati M., Bharati L. (2015). Anti-microbial and anti-diabetic activity of nyctanthes arbor-tristis. *World journal of pharmacy and pharmaceutical sciences, 4*(5), 1031-1040.

Gil, M. I., F. A. Tomás-Barberán, B. Hess-Pierce, D. M. Holcroft and A. A. Kader (2000). Antioxidant activity of pomegranate juice and its relationship with phenolic composition and processing. *Journal of Agricultural and Food chemistry 48*(10): 4581-4589.

Gimbun, J., Pang, S. F., & Yusoff, M. M. (2019). Orthosiphon stamineus (Java Tea). In *Nonvitamin and Nonmineral Nutritional Supplements* (pp. 327-333). Academic Press.

Good, C. B., & Pogach, L. M. (2018). Should Metformin Be First-line Therapy for Patients With Type 2 Diabetes and Chronic Kidney Disease: Informed Patients Should Decide. *JAMA internal medicine*, *178*(7), 911-912.

Grundy, S. M., I. J. Benjamin, G. L. Burke, A. Chait, R. H. Eckel, B. V. Howard, W. Mitch, S. C. Smith Jr and J. R. Sowers (1999). Diabetes and cardiovascular disease: a statement for healthcare professionals from the American Heart Association. *Circulation 100*(10): 1134-1146.

Guo, C., J. Yang, J. Wei, Y. Li, J. Xu and Y. Jiang (2003). Antioxidant activities of peel, pulp and seed fractions of common fruits as determined by FRAP assay. *Nutrition research 23*(12): 1719-1726.

Gupta, R. C., Chang, D., Nammi, S., Bensoussan, A., Bilinski, K., & Roufogalis, B. D. (2017). Interactions between antidiabetic drugs and herbs: an overview of mechanisms of action and clinical implications. *Diabetology & metabolic syndrome*, *9*(1), 59.

Halim, E. M. (2003). Lowering of blood sugar by water extract of Azadirachta indica and Abroma augusta in diabetes rats. *Indian Journal of Experimental Biology*, *41*(6), 636-640.

Halim, M., H. Salleh, W. Mohamed, N. Mat and Y. Yusof (2017). Malaysian traditional medicine: the usage of marine resources as a treatment and complementary medicine for heart disease. *Journal of Fundamental and Applied Sciences 9*(6S): 816-827.

Hamaty, M. (2011). "Insulin treatment for type 2 diabetes: when to start, which to use. *Cleveland Clinic Journal of Medicine 78*(5): 332-342.

Hamilton, G. R. and T. F. Baskett (2000). In the arms of Morpheus: the development of morphine for postoperative pain relief. *Canadian journal of anesthesia 47*(4): 367-374.

Hammes, H.-P., J. Lin, O. Renner, M. Shani, A. Lundqvist, C. Betsholtz, M. Brownlee and U. Deutsch (2002). Pericytes and the pathogenesis of diabetic retinopathy. *Diabetes 51*(10): 3107-3112.

Hanefeld, M. (1998). The role of acarbose in the treatment of non–insulin-dependent diabetes mellitus. *Journal of Diabetes and its Complications*, *12*(4), 228-237.

Hardie, D. G. (2008). Role of AMP-activated protein kinase in the metabolic syndrome and in heart disease. *FEBS letters 582*(1): 81-89.

Harris, E. H. (2005). Elevated liver function tests in type 2 diabetes. *Clinical diabetes 23*(3): 115-119.

Harrison, L. C., & Wentworth, J. M. (2020). Prevention of Autoimmune Disease: The Type 1 Diabetes Paradigm. In *The autoimmune diseases* (pp. 1391-1413). Academic Press.

Hasan, A. M., Redha, A. A., & Mandeel, Q. (2018). Phytochemical Investigations of Pomegranate (Punica granatum) Rind and Aril Extracts and their Antioxidant, Antidiabetic and Antibacterial Activity. *Nat Prod Chem Res*, *6*(332), 2.

Hassan, Z., M. F. Yam, M. Ahmad and A. P. M. Yusof (2010). Antidiabetic properties and mechanism of action of Gynura procumbens water extract in streptozotocin-induced diabetic rats. *Molecules 15*(12): 9008-9023.

He, P., Dong, Z., Wang, Q., Zhan, Q. P., Zhang, M. M., & Wu, H. (2019). Structural characterization and immunomodulatory activity of a polysaccharide from Eurycoma longifolia. *Journal of natural products*, *82*(2), 169-176.

Heitzer, T., Schlinzig, T., Krohn, K., Meinertz, T., & Münzel, T. (2001). Endothelial dysfunction, oxidative stress, and risk of cardiovascular events in patients with coronary artery disease. *Circulation*, *104*(22), 2673-2678.

Henness, S. (2007). Pharmacological interventions in the prevention of type 2 diabetes. *Current Opinion in Endocrinology, Diabetes and Obesity 14*(2): 166-169.

Hesse, U., D. Ysebaert and B. de Hemptinne (2001). Role of somatostatin-14 and its analogues in the management of gastrointestinal fistulae: clinical data. *Gut 49*(suppl 4): iv11-iv20.

Hidjrawan, Y. (2020). Identifikasi senyawa tanin pada daun belimbing wuluh (Averrhoa bilimbi L.). *Jurnal Optimalisasi*, *4*(2), 78-82.

Hosseinzadeh, S., A. Jafarikukhdan, A. Hosseini and R. Armand (2015). The application of medicinal plants in traditional and modern medicine: a review of Thymus vulgaris. *International Journal of Clinical Medicine 6*(09): 635-642.

Hsu, C.-L., B.-H. Hong, Y.-S. Yu and G.-C. Yen (2010). Antioxidant and anti-inflammatory effects of Orthosiphon aristatus and its bioactive compounds. *Journal of Agricultural and Food Chemistry 58*(4): 2150-2156.

Hunaefi, D., Yuliana, N. D., Smetanska, I., & Gruda, N. (2018, November). Effect of ultraviolet and ultrasonic on potential antidiabetic activity of in vitro shoot cultures of Orthosiphon aristatus. In *IOP Conference Series: Earth and Environmental Science* (Vol. 207, No. 1, p. 012008). IOP Publishing.

Husen, R., A. H. L. Pihie and M. Nallappan (2004). Screening for antihyperglycaemic activity in several local herbs of Malaysia. *Journal of Ethnopharmacology 95*(2-3): 205-208.

Ingalls, A. M., M. M. Dickie and G. Snell (1996). Obese, a new mutation in the house mouse. *Obesity research 4*(1): 101-101.

International Diabetes Federation. IDF Diabetes Atlas, 9th edn. Brussels, Belgium: 2019. Available at: http://www.diabetesatlas.org

Inzucchi, S. E., R. M. Bergenstal, J. B. Buse, M. Diamant, E. Ferrannini, M. Nauck, A. L. Peters, A. Tsapas, R. Wender and D. R. Matthews (2012). Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Spectrum 25*(3): 154-171.

Ithnain, N., Panting, A. J., Kassim, R., Amirudin, N., & Krishnan, M. (2020). Perception of Conventional Medicine and Herbal Medicine Usage Amongst Diabetic Patients: A Qualitative Study in Negeri Sembilan, Malaysia. *Global Journal of Health Science, 12*(10), 122-122.

Iranshahy, M., B. Javadi, M. Iranshahi, S. P. Jahanbakhsh, S. Mahyari, F. V. Hassani and G. Karimi (2017). A review of traditional uses, phytochemistry and pharmacology of Portulaca oleracea L. *Journal of Ethnopharmacology 205*: 158-172.

Islam, M. S. and T. du Loots (2009). Experimental rodent models of type 2 diabetes: a review. *Methods and findings in experimental and clinical pharmacology 31*(4): 249-261.

Ismail, M. H. and M. Pinzani (2009). Reversal of liver fibrosis. *Saudi journal of gastroenterology: official journal of the Saudi Gastroenterology Association 15*(1): 72.

Jacob, B., & Narendhirakannan, R. T. (2019). Role of medicinal plants in the management of diabetes mellitus: a review. *3 Biotech*, *9*(1), 4.

JDRF CGM study group. (2008). JDRF randomized clinical trial to assess the efficacy of real-time continuous glucose monitoring in the management of type 1 diabetes: research design and methods. *Diabetes technology & therapeutics*, *10*(4), 310-321.

Jelodar Gholamali, A., M. Maleki, M. Motadayen and S. Sirus (2005). Effect of fenugreek, onion and garlic on blood glucose and histopathology of pancreas of alloxan-induced diabetic rats. *Indian J Med Sci 59*: 64-69.

Jia, G., A. K. Mitra, D. M. Gangahar and D. K. Agrawal (2010). Insulin-like growth factor-1 induces phosphorylation of PI3K-Akt/PKB to potentiate proliferation of smooth muscle cells in human saphenous vein. *Experimental and molecular pathology 89*(1): 20-26.

Jiang, H., H. Zhu, J.-Z. Wang, B. Fu, Y. Lü, Q. Hong, Y. Xie and X. Chen (2011). Tissue inhibitor of metalloproteinase-1 counteracts glucolipotoxicity in the pancreatic β-cell line INS-1. *Chinese medical journal 124*(2): 258-261.

Joussen, A. M., V. Poulaki, M. L. Le, K. Koizumi, C. Esser, H. Janicki, U. Schraermeyer, N. Kociok, S. Fauser and B. Kirchhof (2004). A central role for inflammation in the pathogenesis of diabetic retinopathy. *The FASEB journal 18*(12): 1450-1452.

Junge, B., M. Matzke and J. Stoltefuss (1996). Chemistry and structure-activity relationships of glucosidase inhibitors. *Oral Antidiabetics, Springer:* 411-482.

Junod, A., A. Lambert, L. Orci, R. Pictet, A. Gonet and A. Renold (1967). Studies of the diabetogenic action of streptozotocin. *Proceedings of the Society for Experimental Biology and Medicine 126*(1): 201-205.

Kalaivanan, K. and K. V. Pugalendi (2011). Antihyperglycemic effect of the alcoholic seed extract of Swietenia macrophylla on streptozotocin-diabetic rats. *Pharmacognosy research 3*(1): 67.

Kalavathy Gengiah, R. H. and J. Anbu (2014). Antidiabetic antihyperlipidemic and hepato-protective effect of Gluconorm-5: A polyherbal formulation in steptozotocin induced hyperglycemic rats. *Ancient science of life 34*(1): 23.

Kaneto, H., N. Katakami, M. Matsuhisa and T.-a. Matsuoka (2010). Role of reactive oxygen species in the progression of type 2 diabetes and atherosclerosis. *Mediators of inflammation, 2010.*

Karim, M., M. Islam, S. M. Sarkar, A. Murugan, E. A. Makky, S. Rashid and M. M. Yusoff (2014). Anti-amylolytic activity of fresh and cooked okra (Hibiscus esculentus L.) pod extract. *Biocatalysis and Agricultural Biotechnology 3*(4): 373-377.

Katz, S. R., R. A. Newman and E. P. Lansky (2007). Punica granatum: heuristic treatment for diabetes mellitus. *Journal of medicinal food 10*(2): 213-217.

Kavitha, R (2019). Effect of ethanolic extracts of Indian medicinal plants on the non-enzymatic antioxidant system in streptozotocin induced diabetic rats in comparison with Glibenclamide. *Int J Pharm Sci & Res 10*(1): 418-30.

Kawano, H., Motoyama, T., Hirashima, O., Hirai, N., Miyao, Y., Sakamoto, T., & Yasue, H. (1999). Hyperglycemia rapidly suppresses flow-mediated endothelium-dependent vasodilation of brachial artery. *Journal of the American College of Cardiology, 34*(1), 146-154.

Kazeem, M. I. and A. O. T. Ashafa (2017). Kinetics of inhibition of carbohydrate-metabolizing enzymes and mitigation of oxidative stress by Eucomis humilis Baker bulb. *Beni-Suef University Journal of Basic and Applied Sciences 6*(1): 57-63.

Kazeem, M. I., M. A. Akanji and M. T. Yakubu (2015). Amelioration of pancreatic and renal derangements in streptozotocin-induced diabetic rats by polyphenol extracts of Ginger (Zingiber officinale) rhizome. *Pathophysiology 22*(4): 203-209.

Kesari, A. N., S. Kesari, S. K. Singh, R. K. Gupta and G. Watal (2007). Studies on the glycemic and lipidemic effect of Murraya koenigii in experimental animals. *Journal of Ethnopharmacology 112*(2): 305-311.

Khajebishak, Y., Payahoo, L., Alivand, M., Hamishehkar, H., Mobasseri, M., Ebrahimzadeh, V., & Alipour, B. (2019). Effect of pomegranate seed oil supplementation on the GLUT-4 gene expression and glycemic control in obese people with type 2 diabetes: A randomized controlled clinical trial. *Journal of Cellular Physiology*, *234*(11), 19621-19628.

Khalaf, H., E. Arafat and F. Ghoneim (2019). A histological, immunohistochemical and biochemical study of the effects of pomegranate peel extracts on gibberellic acid induced oxidative stress in adult rat testes. *Biotechnic & Histochemistry 94*(8): 569-582.

Khalil, E. A. (2004). Antidiabetic effect of an aqueous extract of Pomegranate (Punica granatum L.) peels in normal and alloxan diabetic rats. *The Egyptian Journal of Hospital Medicine 16*(1): 92-99.

Khan, A. and J. Pessin (2002). Insulin regulation of glucose uptake: a complex interplay of intracellular signalling pathways. *Diabetologia 45*(11): 1475-1483.

Khanam, Z., Wen, C. S., & Bhat, I. U. H. (2015). Phytochemical screening and antimicrobial activity of root and stem extracts of wild Eurycoma longifolia Jack (Tongkat Ali). *Journal of King Saud University-Science, 27*(1), 23-30.

Kim, C., K. M. Newton and R. H. Knopp (2002). Gestational diabetes and the incidence of type 2 diabetes: a systematic review. *Diabetes care 25*(10): 1862-1868.

Kim, W. and J. M. Egan (2008). The role of incretins in glucose homeostasis and diabetes treatment. *Pharmacological reviews 60*(4): 470-512.

Kim, Y. M., Jeong, Y. K., Wang, M. H., Lee, W. Y., & Rhee, H. I. (2005). Inhibitory effect of pine extract on α-glucosidase activity and postprandial hyperglycemia. *Nutrition 21*(6): 756-761.

Knowler, W. C., E. Barrett-Connor, S. E. Fowler, R. F. Hamman, J. M. Lachin, E. A. Walker and D. M. Nathan (2002). Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *The New England journal of medicine 346*(6): 393-403.

Krentz, A. J., & Bailey, C. J. (2005). Oral Diabetic Agents Current Role in Type 2 Diabetes Melitus. *Riview Article, 65*(3), 394.

Laakso, M. (2010). Cardiovascular disease in type 2 diabetes from population to man to mechanisms: the Kelly West Award Lecture 2008. *Diabetes care 33*(2): 442-449.

Lansky, E. P. and R. A. Newman (2007). Punica granatum (pomegranate) and its potential for prevention and treatment of inflammation and cancer. *Journal of ethnopharmacology 109*(2): 177-206.

Lansky, E., Shubert, S., & Neeman, I. (2000). Pharmacological and therapeutic properties of pomegranate. In *Symposium on production, processing and marketing of pomegranate in the Mediterranean region: advances in research and technology. Séminaires Méditerranéens (CIHEAM). PP* (pp. 231-235).

Larsson, S. C., A. Wallin, N. Håkansson, O. Stackelberg, M. Bäck and A. Wolk (2018). Type 1 and type 2 diabetes mellitus and incidence of seven cardiovascular diseases. *International journal of cardiology 262*: 66-70.

Lau, C. H., Chan, C. M., Chan, Y. W., Lau, K. M., Lau, T. W., Lam, F. C., & Lau, C. B. S. (2008). In vitro antidiabetic activities of five medicinal herbs used in Chinese medicinal formulae. *Phytotherapy Research: An International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives, 22*(10), 1384-1388.

Lawag, I. L., Aguinaldo, A. M., Naheed, S., & Mosihuzzaman, M. (2012). α-Glucosidase inhibitory activity of selected Philippine plants. *Journal of ethnopharmacology, 144*(1), 217-219.

Lebovitz, H. E. (1997). Alpha-glucosidase inhibitors. *Endocrinology and metabolism clinics of North America, 26*(3), 539-551.

Lenzen, S. (2008). The mechanisms of alloxan-and streptozotocin-induced diabetes. *Diabetologia 51*(2): 216-226.

Letchuman, G., W. Wan Nazaimoon, W. Wan Mohamad, L. Chandran, G. Tee, H. Jamaiyah, M. Isa, H. Zanariah, I. Fatanah and Y. Ahmad Faudzi (2010). Prevalence of diabetes in the Malaysian national health morbidity survey III 2006. *Med J Malaysia 65*(3): 180-186.

Levitan, E. B., Y. Song, E. S. Ford and S. Liu (2004). Is nondiabetic hyperglycemia a risk factor for cardiovascular disease?: a meta-analysis of prospective studies. *Archives of internal medicine 164*(19): 2147-2155.

Li, J. W.-H. and J. C. Vederas (2009). Drug discovery and natural products: end of an era or an endless frontier. *Science 325*(5937): 161-165.

Li, Y., C. Guo, J. Yang, J. Wei, J. Xu and S. Cheng (2006). Evaluation of antioxidant properties of pomegranate peel extract in comparison with pomegranate pulp extract. *Food chemistry 96*(2): 254-260.

Li, Y., S. Wen, B. P. Kota, G. Peng, G. Q. Li, J. Yamahara and B. D. Roufogalis (2005). Punica granatum flower extract, a potent α-glucosidase inhibitor, improves postprandial hyperglycemia in Zucker diabetic fatty rats. *Journal of Ethnopharmacology 99*(2): 239-244.

Lin, Z., H. Tian, K. S. Lam, S. Lin, R. C. Hoo, M. Konishi, N. Itoh, Y. Wang, S. R. Bornstein and A. Xu (2013). Adiponectin mediates the metabolic effects of FGF21 on glucose homeostasis and insulin sensitivity in mice. *Cell metabolism 17*(5): 779-789.

Loizzo, M. R., F. Aiello, M. C. Tenuta, M. Leporini, T. Falco and R. Tundis (2019). Pomegranate (Punica granatum L.). *Nonvitamin and Nonmineral Nutritional Supplements, Elsevier:* 467-472.

Lokman, E. F., Saparuddin, F., Muhammad, H., Omar, M. H., & Zulkapli, A. (2019). Orthosiphon stamineus as a potential antidiabetic drug in maternal hyperglycemia in streptozotocin-induced diabetic rats. *Integrative medicine research, 8*(3), 173-179.

Longtin, R. (2003). The pomegranate: nature's power fruit. *CancerSpectrum Knowledge Environment 95*(5): 346-348.

Lu, H., L. Hao, S. Li, S. Lin, L. Lv, Y. Chen, H. Cui, T. Zi, X. Chu and L. Na (2016). Elevated circulating stearic acid leads to a major lipotoxic effect on mouse pancreatic beta cells in hyperlipidaemia via a miR-34a-5p-mediated PERK/p53-dependent pathway. *Diabetologia 59*(6): 1247-1257.

Lu, T.-H., M.-S. Lai, R. N. Anderson and C.-N. Huang (2007). Diabetes reporting as a cause of death: results from the Translating Research Into Action for Diabetes (TRIAD) study: response to McEwen et al. *Diabetes care 30*(5): e46-e46.

Ludwig, J., D. B. McGILL and K. D. Lindor (1997). Nonalcoholic steatohepatitis. *Journal of gastroenterology and hepatology 12*(5): 398-403.

Mahmood, M. H., Osama, A. K., Makky, E. A., Rahim, M. H., Ali, N. H. M., & Hazrudin, N. D. (2019, October). Phytochemical Screening, antimicrobial and antioxidant efficacy of some plant extracts and their mixtures. In *IOP Conference Series: Earth and Environmental Science* (Vol. 346, No. 1, p. 012003). IOP Publishing.

Mahmoud, M. F. and S. M. Sakr (2013). Hepatoprotective Effect of Bee Propolis in Rat Model of streptozotocin-Induced diabetic hepatotoxicity light and electron microscopic study. *Life Sci J 10*: 2048-2054.

Maiti, A., Dewanjee, S., Jana, G., & Mandal, S. C. (2008). Hypoglycemic effect of Swietenia macrophylla seeds against type II diabetes. *International Journal of Green Pharmacy (IJGP), 2*(4).

Majidi Wizneh, F. and M. Zaini Asmawi (2014). Eurycoma longifolia Jack (Simarubaceae); Advances in Its Medicinal Potentials. *Pharmacognosy Journal 6*(4).

Malik, Z. A., Bhat, J. A., Ballabha, R., Bussmann, R. W., & Bhatt, A. B. (2015). Ethnomedicinal plants traditionally used in health care practices by inhabitants of Western Himalaya. *Journal of ethnopharmacology 172*: 133-144.

Malterud, K. E., I. M. Hanche-Olsen and I. Smith-Kielland (1989). Flavonoids from Orthosiphon spicatus. *Planta medica 55*(06): 569-570.

Manna, P., J. Das, J. Ghosh and P. C. Sil (2010). Contribution of type 1 diabetes to rat liver dysfunction and cellular damage via activation of NOS, PARP, IκBα/NF-κB, MAPKs, and mitochondria-dependent pathways: prophylactic role of arjunolic acid. *Free Radical Biology and Medicine 48*(11): 1465-1484.

Mansor, L. S., E. R. Gonzalez, M. A. Cole, D. J. Tyler, J. H. Beeson, K. Clarke, C. A. Carr and L. C. Heather (2013). Cardiac metabolism in a new rat model of type 2 diabetes using high-fat diet with low dose streptozotocin. *Cardiovascular diabetology 12*(1): 136.

Marchesini, G., M. Brizi, G. Bianchi, S. Tomassetti, E. Bugianesi, M. Lenzi, A. J. McCullough, S. Natale, G. Forlani and N. Melchionda (2001). Nonalcoholic fatty liver disease: a feature of the metabolic syndrome. *Diabetes 50*(8): 1844-1850.

Masuda, T., K. Masuda, S. Shiragami, A. Jitoe and N. Nakatani (1992). Orthosiphol A and B, novel diterpenoid inhibitors of TPA (12-O-tetradecanoylphorbol-13-acetate)-induced inflammation, from Orthosiphon stamineus. *Tetrahedron 48*(33): 6787-6792.

Matsui, T., Tanaka, T., Tamura, S., Toshima, A., Tamaya, K., Miyata, Y., & Matsumoto, K. (2007). α-Glucosidase inhibitory profile of catechins and theaflavins. *Journal of Agricultural and Food Chemistry*, *55*(1), 99-105.

Matough, F. A., S. B. Budin, Z. A. Hamid, N. Alwahaibi and J. Mohamed (2012). The role of oxidative stress and antioxidants in diabetic complications. *Sultan Qaboos University Medical Journal 12*(1): 5.

Mayer, J., Russell, R. E., Bates, M. W., & Dickie, M. M. (1953). Metabolic, nutritional and endocrine studies of the hereditary obesity, diabetes syndrome of mice and mechanism of its development. *Metabolism*, *2*, 9-21.

Meigs, J. B. (2010). Epidemiology of type 2 diabetes and cardiovascular disease: translation from population to prevention: the Kelly West award lecture 2009. *Diabetes care 33*(8): 1865-1871.

Mi, C. N., Li, W., Chen, H. Q., Wang, J., Cai, C. H., Li, S. P., & Dai, H. F. (2019). Two new compounds from the roots of Swietenia macrophylla. *Journal of Asian natural products research*, *21*(10), 1005-1012.

Michael, U. A., B. U. David, C. O. Theophine, F. U. Philip, A. M. Ogochukwu and V. A. Benson (2010). Antidiabetic effect of combined aqueous leaf extract of Vernonia amygdalina and metformin in rats. *Journal of Basic and Clinical Pharmacy 1*(3): 197.

Miguel, M. G., M. A. Neves and M. D. Antunes (2010). Pomegranate (Punica granatum L.): A medicinal plant with myriad biological properties-A short review. *Journal of Medicinal Plants Research 4*(25): 2836-2847.

Mingrone, G., S. Panunzi, A. De Gaetano, C. Guidone, A. Iaconelli, L. Leccesi, G. Nanni, A. Pomp, M. Castagneto and G. Ghirlanda (2012). Bariatric surgery versus conventional medical therapy for type 2 diabetes. *New England Journal of Medicine 366*(17): 1577-1585.

Mo, F.f., B.-h. Lv, T. An, J.n. Miao, J.x. Liu, J. Zhang, Z.y. Zhang, M.-h. Ma, X.-y. Yang and D.d. Zhao (2019). Protective mechanism of punicalagin against endoplasmic reticulum stress in the liver of mice with type 2 diabetes mellitus. *Journal of Functional Foods 56*: 57-64.

Modak, M., P. Dixit, J. Londhe, S. Ghaskadbi and T. P. A. Devasagayam (2007). Recent advances in Indian herbal drug research guest editor: Thomas Paul Asir Devasagayam Indian herbs and herbal drugs used for the treatment of diabetes. *Journal of clinical biochemistry and nutrition 40*(3): 163-173.

Mohamed, E. A. H., A. J. Mohamed, M. Asmawi, A. Sadikun, O. S. Ebrika and M. F. Yam (2011). Antihyperglycemic effect of Orthosiphon stamineus benth leaves extract and its bioassay-guided fractions. *Molecules 16*(5): 3787-3801.

Mohamed, E. A. H., Siddiqui, M. J. A., Ang, L. F., Sadikun, A., Chan, S. H., Tan, S. C., & Yam, M. F. (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), 176.

Mohamed, E. A. H., M. F. Yam, L. F. Ang, A. J. Mohamed and M. Z. Asmawi (2013). Antidiabetic properties and mechanism of action of Orthosiphon stamineus Benth bioactive sub-fraction in streptozotocin-induced diabetic rats. *Journal of acupuncture and meridian studies 6*(1): 31-40.

Mohamed, E. A. H., Siddiqui, M. J. A., Ang, L. F., Sadikun, A., Chan, S. H., Tan, S. C. & Yam, M. F. (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), 176.

Mohamed, E. A., Ahmad, M., Ang, L. F., Asmawi, M., & Yam, M. F. (2015). Evaluation of α-glucosidase inhibitory effect of 50% ethanolic standardized extract of Orthosiphon stamineus benth in normal and streptozotocin-induced diabetic rats. *Evidence-Based Complementary and Alternative Medicine*, *2015*.

Mohamed, Q., M. C. Gillies and T. Y. Wong (2007). Management of diabetic retinopathy: a systematic review. *Jama 298*(8): 902-916.

Motshakeri, M., Ebrahimi, M., Goh, Y. M., Othman, H. H., Hair-Bejo, M., & Mohamed, S. (2014). Effects of brown seaweed (Sargassum polycystum) extracts on kidney, liver, and pancreas of type 2 diabetic rat model. *Evidence-based complementary and alternative medicine*, *2014*.

Mou, K. M. and P. R. Dash (2016). A comprehensive review on Gynura procumbens leaves. *International Journal Of Pharmacognosy 3*(4): 167-174.

Mui, L. D. C., Adeline, T., & Norazah, M. S. (2015). The prevalence of traditional and complementary medicine usage in Sabah, Malaysia. In *6th International Conference on Business and Economics Research* (pp. 1-15).

Munday, R. (1988). Dialuric acid autoxidation: effects of transition metals on the reaction rate and on the generation of "active oxygen" species. *Biochemical pharmacology 37*(3): 409-413.

Nagy, M., M. Bastawy and N. Abdel-Hamid (2012). Effects of Momordica charantia on Streptozotocin-induced diabetes in rats: role of insulin oxidative stress and nitric oxide. *J Health Sci 2*(2): 8-13.

Nobili, V., M. Marcellini, R. Devito, P. Ciampalini, F. Piemonte, D. Comparcola, M. R. Sartorelli and P. Angulo (2006). NAFLD in children: a prospective clinical-pathological study and effect of lifestyle advice. *Hepatology 44*(2): 458-465.

Nomura, F., K. Ohnishi, T. Ochiai and K. Okuda (1987). Obesity-related nonalcoholic fatty liver: CT features and follow-up studies after low-calorie diet. *Radiology 162*(3): 845-847.

Noor, A., S. Gunasekaran, A. S. Manickam and M. Vijayalakshmi (2008). Antidiabetic activity of Aloe vera and histology of organs in streptozotocin-induced diabetic rats. *Current science:* 1070-1076.

Noubiap, J. J., J. R. Nansseu, U. F. Nyaga, J. R. Nkeck, F. T. Endomba, A. D. Kaze, V. N. Agbor and J. J. Bigna (2019). Global prevalence of diabetes in active tuberculosis: a systematic review and meta-analysis of data from 2· 3 million patients with tuberculosis. *The Lancet Global Health 7*(4): e448-e460.

Ohaeri, O. (2001). Effect of garlic oil on the levels of various enzymes in the serum and tissue of streptozotocin diabetic rats. *Bioscience reports 21*(1): 19-24.

Olah, N.-K., L. Radu, C. Mogoşan, D. Hanganu and S. Gocan (2003). Phytochemical and pharmacological studies on Orthosiphon stamineus Benth.(Lamiaceae) hydroalcoholic extracts. *Journal of pharmaceutical and biomedical analysis 33*(1): 117-123.

Olokoba, A. B., O. A. Obateru and L. B. Olokoba (2012). Type 2 diabetes mellitus: a review of current trends. *Oman medical journal 27*(4): 269.

Othman, S. N. N., Lum, P. T., Noor, A. A. M., Mazlan, N. A., Yusri, P. Z. S., Ghazali, N. F., & Sekar, M. (2020). Ten commonly available medicinal plants in Malaysia used for cosmetic formulations–A review. *International Journal of Research in Pharmaceutical Sciences*, *11*(2), 1716-1728.

Pagán, J. A. and J. Tanguma (2007). Health care affordability and complementary and alternative medicine utilization by adults with diabetes. *Diabetes care 30*(8): 2030-2031.

Pan, A., J. Sun, Y. Chen, X. Ye, H. Li, Z. Yu, Y. Wang, W. Gu, X. Zhang and X. Chen (2007). Effects of a flaxseed-derived lignan supplement in type 2 diabetic patients: a randomized, double-blind, cross-over trial. *PLoS One 2*(11): e1148.

Patel, D. K., Kumar, R., Laloo, D., & Hemalatha, S. (2012). Natural medicines from plant source used for therapy of diabetes mellitus: An overview of its pharmacological aspects. *Asian Pacific Journal of Tropical Disease*, *2*(3), 239-250.

Patel, A. N., Bandawane, D. D., & Mhetre, N. K. (2014). Pomegranate (Punica granatum Linn.) leaves attenuate disturbed glucose homeostasis and hyperglycemia mediated hyperlipidemia and oxidative stress in streptozotocin induced diabetic rats. *European Journal of Integrative Medicine*, *6*(3), 307-321.

Pattanayak, P., P. Behera, D. Das and S. K. Panda (2010). Ocimum sanctum Linn. A reservoir plant for therapeutic applications: An overview. *Pharmacognosy reviews 4*(7): 95.

Pick, A., J. Clark, C. Kubstrup, M. Levisetti, W. Pugh, S. Bonner-Weir and K. S. Polonsky (1998). Role of apoptosis in failure of beta-cell mass compensation for insulin resistance and beta-cell defects in the male Zucker diabetic fatty rat. *Diabetes 47*(3): 358-364.

Ponnusamy, S., Ravindran, R., Zinjarde, S., Bhargava, S., & Ravi Kumar, A. (2010). Evaluation of traditional Indian antidiabetic medicinal plants for human pancreatic amylase inhibitory effect in vitro. *Evidence-Based Complementary and Alternative Medicine, 2011*.

Portillo-Sanchez, P., F. Bril, M. Maximos, R. Lomonaco, D. Biernacki, B. Orsak, S. Subbarayan, A. Webb, J. Hecht and K. Cusi (2015). High prevalence of nonalcoholic fatty liver disease in patients with type 2 diabetes mellitus and normal plasma aminotransferase levels. *The journal of clinical endocrinology & metabolism 100*(6): 2231-2238.

Prasad, K. (2002). Suppression of phosphoenolpyruvate carboxykinase gene expression by secoisolariciresinol diglucoside (SDG), a new antidiabetic agent. *International Journal of Angiology 11*(02): 107-109.

Premanath, R., & Nanjaiah, L. (2015). Antidiabetic and Antioxidant potential of Andrographis paniculata Nees. leaf ethanol extract in streptozotocin induced diabetic rats. *Journal of Applied Pharmaceutical Science*, *5*(1), 069-076.

Punasiya, R., A. Joshi and K. Patidar (2010). Antidiabetic Effect of an Aqueous Extract of Pomegranate (Punica granatum L.) Peels in Normal and Alloxan Diabetic Rats. *Research Journal of Pharmacy and Technology 3*(1): 272-274.

Pushparaj, P., C. Tan and B. Tan (2000). Effects of Averrhoa bilimbi leaf extract on blood glucose and lipids in streptozotocin-diabetic rats. *Journal of ethnopharmacology 72*(1-2): 69-76.

Qayyum, R. and L. Greene (2011). AHRQ's comparative effectiveness research on premixed insulin analogues for adults with type 2 diabetes: understanding and applying the systematic review findings. *Journal of Managed Care Pharmacy 17*(3 Supp A): s1-s19.

Quagliaro, L., L. Piconi, R. Assaloni, L. Martinelli, E. Motz and A. Ceriello (2003). Intermittent high glucose enhances apoptosis related to oxidative stress in human umbilical vein endothelial cells: the role of protein kinase C and NAD (P) H-oxidase activation. *Diabetes 52*(11): 2795-2804.

Quattrini, C. and S. Tesfaye (2003). Understanding the impact of painful diabetic neuropathy. *Diabetes/metabolism research and reviews 19*(S1): S2-S8.

Rahimi, R., S. Nikfar, B. Larijani and M. Abdollahi (2005). A review on the role of antioxidants in the management of diabetes and its complications. *Biomedicine & Pharmacotherapy 59*(7): 365-373.

Rajkumar, L., Srinivasan, N., Balasubramanian, K., & Govindarajulu, P. (1991). Increased degradation of dermal collagen in diabetic rats. *Indian journal of experimental biology*, *29*(11), 1081-1083.

Ramesh, B. and K. Pugalendi (2006). Antihyperglycemic effect of umbelliferone in streptozotocin-diabetic rats. *Journal of medicinal food 9*(4): 562-566.

Rehman, S. U., K. Choe and H. H. Yoo (2016). Review on a traditional herbal medicine, Eurycoma longifolia Jack (Tongkat Ali): its traditional uses, chemistry, evidence-based pharmacology and toxicology. *Molecules 21*(3): 331.

Reyes, B., N. Bautista, N. Tanquilut, R. Anunciado, A. Leung, G. Sanchez, R. Magtoto, P. Castronuevo, H. Tsukamura and K.-I. Maeda (2006). Anti-diabetic potentials of Momordica charantia and Andrographis paniculata and their effects on estrous cyclicity of alloxan-induced diabetic rats. *Journal of ethnopharmacology 105*(1-2): 196-200.

Rifaai, R., N. El-Tahawy, E. A. Saber and R. Ahmed (2012). Effect of quercetin on the endocrine pancreas of the experimentally induced diabetes in male albino rats: a histological and immunohistochemical study. *J Diabetes Metab 3*(182): 2.

Röder, P. V., Geillinger, K. E., Zietek, T. S., Thorens, B., Koepsell, H., & Daniel, H. (2014). The role of SGLT1 and GLUT2 in intestinal glucose transport and sensing. *PloS one, 9*(2).

Röder, P. V., Wu, B., Liu, Y., & Han, W. (2016). Pancreatic regulation of glucose homeostasis. *Experimental & molecular medicine, 48*(3), e219-e219.

Rosenfeld, L. (2002). Insulin: discovery and controversy. *Clinical chemistry 48*(12): 2270-2288.

Roy, A., R. Geetha and T. Lakshmi (2011). Averrhoa bilimbi Linn–Nature's Drug Store-A Pharmacological Review. *Int J Drug Dev Res 3*: 101-106.

Saad, E. A., Hassanien, M. M., El-Hagrasy, M. A., & Radwan, K. H. (2015). Antidiabetic, hypolipidemic and antioxidant activities and protective effects of Punica granatum peels powder against pancreatic and hepatic tissues injuries in streptozotocin induced IDDM in rats. *Int J Pharm Pharm Sci, 7*(7), 397-402.

Saddiq, A. A., & Mohamed, A. M. M. (2019). Rescue of inflammatory renal damage by medicinal plant extracts in diabetic rats. *Int J Life Sci Pharma Res, 9*, 24-33.

Saklani, A. and S. K. Kutty (2008). Plant-derived compounds in clinical trials. *Drug discovery today 13*(3-4): 161-171.

Salahuddin, M., S. S. Jalalpure and N. B. Gadge (2010). Antidiabetic activity of aqueous bark extract of Cassia glauca in streptozotocin-induced diabetic rats. *Canadian journal of physiology and pharmacology 88*(2): 153-160.

Samuel, A. J. S. J., A. Kalusalingam, D. K. Chellappan, R. Gopinath, S. Radhamani, H. A. Husain, V. Muruganandham and P. Promwichit (2010). Ethnomedical survey of plants used by the Orang Asli in Kampung Bawong, Perak, West Malaysia. *Journal of ethnobiology and ethnomedicine 6*(1): 5.

Pramono, S., & Nugroho, A. E. (2015). Effect of herbal combination of Andrographis paniculata (Burm. f) Ness and Gynura procumbens (Lour.) Merr ethanolic extracts in alloxan-induced hyperglycemic rats. *International Food Research Journal*, *22*(4).

Sathiavelu, A., Sangeetha, S., Archit, R., & Mythili, S. (2013). In vitro anti-diabetic activity of aqueous extract of the medicinal plants Nigella sativa, Eugenia jambolana, Andrographis paniculata and Gymnema sylvestre. *Int. J. Drug Dev. Res*, *5*(2), 323-328.

Seino, S. (2013). A novel rat model of type 2 diabetes: the Zucker fatty diabetes mellitus ZFDM rat. *Journal of diabetes research*, *2013*.

Serrano-Martín, X., G. Payares and A. Mendoza-León (2006). Glibenclamide, a blocker of K+ ATP channels, shows antileishmanial activity in experimental murine cutaneous leishmaniasis. *Antimicrobial agents and chemotherapy 50*(12): 4214-4216.

Shahkoomahally, S., Khadivi, A., Brecht, J. K., & Sarkhosh, A. (2020). Chemical and physical attributes of fruit juice and peel of pomegranate genotypes grown in Florida, USA. *Food Chemistry*, 128302.

Sivakumar et al. (2011). Effective natural dye extraction from different plant materials using ultrasound. *Industrial Crops and Products 33*(1): 116-122.

Sobngwi, E., F. Mauvais-Jarvis, P. Vexiau, J.-C. Mbanya and J.-F. Gautier (2001). Diabetes in africans. *Studies 6*: 34.

Sotoudeh, R., Mousa-Al-Reza Hadjzadeh, Z. G., & Aghaei, A. (2019). The anti-diabetic and antioxidant effects of a combination of Commiphora mukul, Commiphora myrrha and Terminalia chebula in diabetic rats. *Avicenna journal of phytomedicine*, *9*(5), 454.

Sowka, J. W., Gurwood, A. S., & Kabat, A. G. (2001). Optic nerve head drusen. *Handbook of Ocular Disease Management*.

Spiller, H. A. and T. S. Sawyer (2006). Toxicology of oral antidiabetic medications. *American journal of health-system pharmacy 63*(10): 929-938.

Srinivasan, K. and P. Ramarao (2007). Animal model in type 2 diabetes research: An overview. *Indian Journal of Medical Research 125*(3): 451.

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

Standl, E., Theodorakis, M. J., Erbach, M., Schnell, O., & Tuomilehto, J. (2014). On the potential of acarbose to reduce cardiovascular disease. *Cardiovascular diabetology*, *13*(1), 81.

Stanifer, J. W., U. D. Patel, F. Karia, N. Thielman, V. Maro, D. Shimbi, H. Kilaweh, M. Lazaro, O. Matemu and J. Omolo (2015). The determinants of traditional medicine use in northern Tanzania: a mixed-methods study. *PloS one 10*(4): e0122638.

Subramanian, R., Asmawi, M. Z., & Sadikun, A. (2008). In vitro alpha-glucosidase and alpha-amylase enzyme inhibitory effects of Andrographis paniculata extract and andrographolide. *Acta Biochim Pol, 55*(2), 391-398.

Sukweenadhi, J., Yunita, O., Setiawan, F., Siagian, M. T., & Avanti, C. (2020). Antioxidant activity screening of seven Indonesian herbal extract. *Biodiversitas Journal of Biological Diversity, 21*(5).

Sumaryono, W., P. Proksch, V. Wray, L. Witte and T. Hartmann (1991). Qualitative and quantitative analysis of the phenolic constituents from Orthosiphon aristatus. *Planta medica 57*(02): 176-180.

Szkudelski, T. (2012). Streptozotocin–nicotinamide-induced diabetes in the rat. Characteristics of the experimental model. *Experimental biology and medicine 237*(5): 481-490.

Takaya, K., Y. Ogawa, N. Isse, T. Okazaki, N. Satoh, H. Masuzaki, K. Mori, N. Tamura, K. Hosoda and K. Nakao (1996). Molecular cloning of rat leptin receptor isoform complementary DNAs-identification of a missense mutation in Zucker fatty (fa/fa) rats. *Biochemical and biophysical research communications 225*(1): 75-83.

Talbott, S. M. (2019). Human performance and sports applications of Tongkat Ali (Eurycoma longifolia). *Nutrition and Enhanced Sports Performance, Elsevier:* 729-734.

Tamura, S. and I. Shimomura (2005). Contribution of adipose tissue and de novo lipogenesis to nonalcoholic fatty liver disease. *The Journal of clinical investigation 115*(5): 1139-1142.

Tan, B. K. H., C. H. Tan and P. N. Pushparaj (2005). Anti–diabetic activity of the semi–purified fractions of Averrhoa bilimbi in high fat diet fed–streptozotocin–induced diabetic rats. *Life sciences 76*(24): 2827-2839.

Tan, H.-L., K.-G. Chan, P. Pusparajah, L.-H. Lee and B.-H. Goh (2016). Gynura procumbens: an overview of the biological activities. *Frontiers in pharmacology* 7: 52.

Tesauro, M., & Mazzotta, F. A. (2020). Pathophysiology of diabetes. In *Transplantation, Bioengineering, and Regeneration of the Endocrine Pancreas* (pp. 37-47). Academic Press.

Tezuka, Y., P. Stampoulis, A. H. Banskota, S. Awale, K. Q. Tran, I. Saiki and S. Kadota (2000). Constituents of the Vietnamese medicinal plant Orthosiphon stamineus. *Chemical and Pharmaceutical Bulletin 48*(11): 1711-1719.

Thu, H. E., Z. Hussain, I. N. Mohamed and A. N. Shuid (2018). Exploring dynamic biomedical algorithm of Eurycoma longifolia Jack and its bioactive phytochemicals: A review of pharmacokinetic and pharmacodynamic implications and future prospects. *Asian Pacific Journal of Tropical Medicine 11*(2): 89.

Tian, L., X. Teng, C. Zhong and Y. Xie (2015). Chemical Constituents from the Barks of Swietenia macrophylla. *General Chemistry 1*(1).

Tolman, K. G., V. Fonseca, A. Dalpiaz and M. H. Tan (2007). Spectrum of liver disease in type 2 diabetes and management of patients with diabetes and liver disease. *Diabetes care 30*(3): 734-743.

Trevelyan, J. (1993). Complementary medicine. Herbal medicine. *Nursing times 89*(43): 36-38.

Tripathi, A. C., S. J. Gupta, G. N. Fatima, P. K. Sonar, A. Verma and S. K. Saraf (2014). 4-Thiazolidinones: the advances continue. *European Journal of Medicinal Chemistry 72*: 52-77.

Tzeng, T.-F., S.-S. Liou, C. J. Chang and I.-M. Liu (2013). Zerumbone, a tropical ginger sesquiterpene, ameliorates streptozotocin-induced diabetic nephropathy in rats by reducing the hyperglycemia-induced inflammatory response. *Nutrition & metabolism 10*(1): 64.

Utzschneider, K. M. and S. E. Kahn (2006). The role of insulin resistance in nonalcoholic fatty liver disease. *The Journal of Clinical Endocrinology & Metabolism 91*(12): 4753-4761.

Valentovic, M. A., N. Alejandro, A. B. Carpenter, P. I. Brown and K. Ramos (2006). Streptozotocin (STZ) diabetes enhances benzo (α) pyrene induced renal injury in Sprague Dawley rats. *Toxicology letters 164*(3): 214-220.

Van De Laar, F. A., Lucassen, P. L., Akkermans, R. P., Van De Lisdonk, E. H., Rutten, G. E., & Van Weel, C. (2005). α-Glucosidase inhibitors for patients with type 2 diabetes: results from a Cochrane systematic review and meta-analysis. *Diabetes care*, *28*(1), 154-163.

Wang, B., P. Charukeshi Chandrasekera and J. J Pippin (2014). Leptin-and leptin receptor-deficient rodent models: relevance for human type 2 diabetes. *Current diabetes reviews 10*(2): 131-145.

Wang, L., L. Guo, L. Zhang, Y. Zhou, Q. He, Z. Zhang and M. Wang (2013). Effects of glucose load and nateglinide intervention on endothelial function and oxidative stress. *Journal of diabetes research, 2013.*

Wang, Q., R. Somwar, P. J. Bilan, Z. Liu, J. Jin, J. R. Woodgett and A. Klip (1999). Protein kinase B/Akt participates in GLUT4 translocation by insulin in L6 myoblasts. *Molecular and cellular biology 19*(6): 4008-4018.

Wanless, I. R. and J. S. Lentz (1990).Fatty liver hepatitis (steatohepatitis) and obesity: an autopsy study with analysis of risk factors. *Hepatology 12*(5): 1106-1110.

Watson, R. T., M. Kanzaki and J. E. Pessin (2004). Regulated membrane trafficking of the insulin-responsive glucose transporter 4 in adipocytes. *Endocrine reviews 25*(2): 177-204.

Weir, G. C. and S. Bonner-Weir (2004). Five stages of evolving beta-cell dysfunction

during progression to diabetes. *Diabetes 53*(suppl 3): S16-S21.

Wherrett, D. K. and D. Daneman (2009). Prevention of type 1 diabetes. *Endocrinology and Metabolism Clinics 38*(4): 777-790.

Wild, S., G. Roglic, A. Green, R. Sicree and H. King (2004). Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes care 27*(5): 1047-1053.

Worthley, L. (2003). The Australian short course on intensive care medicine. *Handbook, Gillingham printers, South Australia.* pp: 31-55.

Wu, M., S. Li, X. Yu, W. Chen, H. Ma, C. Shao, Y. Zhang, A. Zhang, S. Huang and Z. Jia (2019). Mitochondrial activity contributes to impaired renal metabolic homeostasis and renal pathology in STZ-induced diabetic mice. *American Journal of Physiology-Renal Physiology 317*(3): F593-F605.

Xia, Y., Z. Xie, G. Huang and Z. Zhou (2019). Incidence and trend of type 1 diabetes and the underlying environmental determinants. *Diabetes/metabolism research and reviews 35*(1): e3075.

Xin, H. G., Zhang, B. B., Wu, Z. Q., Hang, X. F., Xu, W. S., Ni, W., & Miao, X. H. (2014). Treatment with baicalein attenuates methionine-choline deficient diet-induced non-alcoholic steatohepatitis in rats. *European Journal of Pharmacology, 738*, 310-318.

Xu, H., Barnes, G. T., Yang, Q., Tan, G., Yang, D., Chou, C. J., & Chen, H. (2003). Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. *The Journal of clinical investigation, 112*(12), 1821-1830.

Yahya, F., S. Mamat, M. Kamarolzaman, A. Seyedan, K. Jakius, N. Mahmood, M. Shahril, Z. Suhaili, N. Mohtarrudin and D. Susanti (2013). Hepatoprotective activity of methanolic extract of Bauhinia purpurea leaves against paracetamol-induced hepatic damage in rats. *Evidence-Based Complementary and Alternative Medicine, 2013.*

Yang, L. X., Liu, T. H., Huang, Z. T., Li, J. E., & Wu, L. L. (2011). Research progress on the mechanism of single-Chinese medicinal herbs in treating diabetes mellitus. *Chinese journal of integrative medicine, 17*(3), 235-240.

Yashchenko, A. M., L. V. Pankevych and A. D. Lutsyk (2012). Rat liver carbohydrate alterations in streptozotocin-induced diabetic rats. *Eur J Anat 16*(2): 82-90.

Yoon, J. W. and H. S. Jun (2001). Cellular and molecular pathogenic mechanisms of insulin-dependent diabetes mellitus. *Annals of the New York Academy of Sciences 928*(1): 200-211.

Zafar, M. and S. N.-u.-H. Naqvi (2010). Effects of STZ-Induced Diabetes on the Relative Weights of Kidney, Liver and Pancreas in Albino Rats: A Comparative Study. *International Journal of Morphology 28*(1).

Zari, T. A. and M. A. Al-Thebaiti (2018). Effects of Caralluma russeliana stem extract on some physiological parameters in streptozotocin-induced diabetic male rats. *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy 11*: 619.

Zheng, Y., S. H. Ley and F. B. Hu (2018). Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. *Nature Reviews Endocrinology 14*(2): 88.

Zia, T., S. N. Hasnain and S. Hasan (2001). Evaluation of the oral hypoglycaemic effect of Trigonella foenum-graecum L.(methi) in normal mice. *Journal of ethnopharmacology 75*(2-3): 191-195.

Zucker, L. M. and T. F. Zucker (1961). Fatty, a new mutation in the rat. *Journal of Heredity 52*(6): 275-278.