UNIVERSITI PUTRA MALAYSIA

EVALUATION OF SYNERGISTIC ANTIDIABETIC ACTIVITY *IN VITRO* AND *IN VIVO* OF *Taraxacum officinale* (L.) Weber Ex F.H.Wigg AND *Momordica charantia* L. DUAL HERBAL COMBINATION

NITHIYAA A/P PERUMAL

FS 2021 37

EVALUATION OF SYNERGISTIC ANTIDIABETIC ACTIVITY *IN VITRO* AND *IN VIVO* OF *Taraxacum officinale* (L.) Weber Ex F.H.Wigg AND *Momordica charantia* L. DUAL HERBAL COMBINATION

By

NITHIYAA A/P PERUMAL

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

June 2021

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

EVALUATION OF SYNERGISTIC ANTIDIABETIC ACTIVITY *IN VITRO* AND *IN VIVO* OF *Taraxacum officinale* (L.) Weber Ex F.H.Wigg AND *Momordica charantia* L. DUAL HERBAL COMBINATION

By

NITHIYAA A/P PERUMAL

June 2021

Chair : Meenakshii Nallappan, PhD
Faculty : Science

Diabetes type 2 is the most common type of diabetes, which accounts for 90% of most diabetes cases. Many commercial drugs were used to treat this disease, however these drugs come with adverse side effects and eventually all of them fail to restore the normal glycemic control in patients. Therefore, the search for a more effective antidiabetic agent preferably from dietary source, which is economical and non-toxic or less toxic was considered. Many herbal plants have been found to show multiple antidiabetic activities when used alone or in combination. Therefore, the dual herbal combination of *Taraxacum officinale* (L.) Weber ex F.H.Wigg and *Momordica charantia* L. crude extracts were chosen in this study owing to the numerous antidiabetic compounds present in both plant extracts. Basically, the dried and ground samples of *T. officinale* (whole plant) and *M. charantia* (fruit) were extracted with Soxhlet apparatus using a range of non-polar solvents (petroleum ether, chloroform and ethyl acetate) and polar solvents (acetone, ethanol and water) separately. The extracts were screened for Total Phenolic Content (TPC), Total Flavonoid Content (TFC) and 2,2-diphenyl-1-picrylhydrazyl (DPPH) scavenging activity. The antidiabetic properties of the extracts were assessed via glucose uptake assay using L6 muscle cells, dipeptidyl peptidase-4 (DPP-4), α-amylase and α-glucosidase inhibition activity via enzyme-substrate based reaction assays as well as *in vivo* acute toxicology, oral glucose tolerance test (OGTT) and a 28-day antidiabetic study in a streptozotocin-nicotinamide (STZ-NA) induced diabetic rat model. Based on this study, the polar extracts of both *T. officinale* and *M. charantia* recorded higher phytochemical contents and increased DPPH scavenging activity compared to the non-polar extracts. The ethanolic extracts of both *T. officinale* and *M. charantia* showed optimum antidiabetic properties (ANOVA, $p<0.05$). Therefore, both these ethanolic extracts were combined in the ratio of

1:1 to further assess it synergistic antidiabetic activity. The dual herbal combination proved to exert better antidiabetic properties compared to the single extracts of *T. officinale* and *M. charantia* since there was a significant (ANOVA, $p<0.05$) increase in percentage inhibition of DPP-4, α-amylase and α-glucosidase enzymes. The percentage inhibition of DPP-4 of the dual herbal combination was 81.34±0.07, compared to 43.69±0.56 and 14.62±0.81 percent as recorded by both *T. officinale* and *M. charantia* respectively. The IC_{50} values recorded by the dual herbal combination towards α-amylase and α-glucosidase enzymes were 2.77±0.16 and 28.82±0.67 mg/ml respectively, which was significantly (ANOVA, $p<0.05$) the lowest value in comparison to the single extracts. However, the dual herbal combination was noted to show a moderate glucose uptake activity, since there was no significant difference (ANOVA, $p>0.05$) compared to the single extract of *T. officinale* but a significantly (ANOVA, $p<0.05$) lower glucose uptake activity when compared to the single extract of *M. charantia*. As for the *in vivo* study, the dual herbal combination was proved non-toxic as none of the test animals showed any symptoms of poisoning or toxicity. The dual herbal combination tested *in vivo* on STZ-NA induced diabetic rat model showed blood glucose lowering activity of the test sample at 250 mg/kg body weight (b.w) were comparable to that of Glibenclamide (1 mg/kg b.w), where the blood glucose level was significantly (ANOVA, $p<0.05$) restored within 60 minutes post glucose administration during OGTT. Besides, at the end of the 28-days antidiabetic study, it was shown that the antihyperglycemic activity of the dual herbal combination at 250 mg/kg b.w was also comparable to all three positive drugs, namely, Glibenclamide (1 mg/kg), Metformin (50 mg/kg) and Sitagliptin (10 mg/kg), because, under these treatments, the hyperglycemic condition of the test animals was not aggravated throughout the entire four weeks of study. The presence of various polyphenol compounds such as caffeic acid and taraxacin in *T. officinale* and charantin and polypeptide-p in *M. charantia* have contributed to the various antidiabetic properties in the respective ethanolic extracts, hence showing an improved antidiabetic activity upon combination both *in vitro* and *in vivo*. The combined synergistic activities of these two plants in displaying antidiabetic activities proves to be a potential dual herbal combination which is safe and less toxic to manage Type 2 Diabetes Mellitus.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Doktor Falsafah

PENILAIAN AKTIVITI ANTIDIABETIK SINERGISTIK *IN VITRO* DAN *IN VIVO* KOMBINASI DWIHERBA *Taraxacum officinale* (L.) Weber Ex F.H.Wigg DAN *Momordica charantia* L.

Oleh

NITHIYAA A/P PERUMAL

Jun 2021

Pengerusi : Meenakshii Nallappan, PhD
Fakulti : Sains

Penyakit Diabetes mellitus Jenis 2 merupakan kelas diabetik yang amat kerap dan merangkumi 90% daripada keseluruhan kes-kes diabetik. Terdapat pelbagai jenis ubat komersial yang digunakan bagi tujuan merawat penyakit ini, namun ubat-ubatan ini didapati menyebabkan berbagai jenis kesan sampingan yang tidak diingini dan lama kelamaan, ubatan ini didapati gagal mengekalkan aras glikemia yang normal dikalangan pesakit. Oleh yang demikian, penerokaan agen antidiabetik daripada sumber pemakanan yang lebih ekonomi and tidak bertoksik amat dipertimbangkan. Pelbagai jenis tumbuhan herba telah dijumpai yang menunjukkan pelbagai sifat antidiabetik samada digunakan secara tunggal mahupun secara gabungan dwiherba. Oleh itu, gabungan dwiherba di antara ekstrak *Taraxacum officinale* (L.) Weber ex F.H.Wigg dan *Momordica charantia* L. dipilih dalam kajian ini oleh kerana kedua-dua tumbuhan herba ini terbukti kaya dengan kehadiran pelbagai jenis kompaun antidiabetik. Secara ringkasnya, sampel *T. officinale* (keseluruhan tumbuhan) dan *M. charantia* (buah) yang telah pun dikeringkan dan dikisar, diekstrak menggunakan pelarut-pelarut organik iaitu petroleum eter, kloroform, etil asetat, aseton, etanol dan air suling secara berasingan. Kesemua ekstrak ini disaring untuk menentukan jumlah kandungan fenolik (TPC), jumlah kandungan flavonoid (TFC) dan aktiviti perencatan 2,2-diphenyl-1-picrylhydrazyl (DPPH). Sifat antidiabetik ekstrak-ekstrak ini dinilai menerusi ujian penyerapan glukosa oleh titisan sel otot L6, aktiviti perencatan terhadap enzim dipeptidyl peptidase-4 (DPP-4), α-amilase dan α-glukosidase melalui tindak balas berasaskan enzim-substrat, serta ujian *in vivo* yang melibatkan ujian ketoksikan akut, glukosa tolerans (OGTT) dan kajian antidiabetes selama 28 hari yang melibatkan model tikus diabetes teraruh streptozotocin-nicotinamide (STZ-NA). Berdasarkan kajian ini, extract polar dari kedua-dua *T. officinale* dan *M. charantia* mencatatkan kandungan fitokimia yang

lebih tinggi serta peningkatan activiti perencatan DPPH, berbanding dengan ekstrak bukan polar. Ekstrak etanol dari kedua-dua *T. officinale* dan *M. charantia* menunjukkan sifat antidiabetik yang optimum (ANOVA, $p<0.05$). Oleh itu, kedua-dua ekstrak etanol ini digabungkan dalam nisbah 1:1, seterusnya aktiviti antidiabetes sinergi dinilai. Kombinasi dwiherba ini terbukti mempunyai sifat antidiabetik yang lebih baik berbanding ekstrak etanol tunggal kedua-dua *T. officinale* dan *M. charantia*, kerana terdapat peningkatan peratus perencatan enzim DPP-4, α-amilase dan α-glukosidase yang ketara (ANOVA, $p<0.05$). Peratus perencatan DPP-4 oleh kombinasi dwiherba ini adalah 81.34±0.07, berbanding dengan 43.69±0.56 dan 14.62±0.81 peratus yang dicatatkan oleh kedua-dua ekstrak tunggal *T. officinale* dan *M. charantia*. Nilai IC_{50} yang dicatat oleh kombinasi dwiherba ke arah enzim α-amilase dan α-glukosidase adalah 2.77 ± 0.16 dan 28.82 ± 0.67 mg/ml, iaitu nilai terendah yang amat ketara (ANOVA, $p<0.05$) berbanding dengan ekstrak-ekstrak tunggal. Walau bagaimanapun, kombinasi dwiherba ini menunjukkan aktiviti penyerapan glukosa yang sederhana, kerana tiada perbezaan yang ketara (ANOVA, $p>0.05$) berbanding ekstrak etanol tunggal *T. Officinale*, namun terdapat perbezaan yang ketara (ANOVA, $p<0.05$) berbanding ekstrak etanol tunggal *M. Charantia* di mana aktiviti penyerapan glukosa adalah lebih rendah. Dalam ujian ketoksikan akut *in vivo*, kombinasi dwiherba terbukti tidak bertoksik kerana tiada sebarang haiwan pelakuan dalam ujian ini menunjukkan ciri-ciri keracunan atau ketoksikan. Kombinasi dwiherba ini apabila diuji menggunakan ujian OGTT melalui *in vivo* terhadap model tikus teraruh diabetes STZ-NA, activiti pengurangan glukosa dalam darah oleh kombinasi dwiherba pada kepekatan 250 mg/kg berat tubuh (b) adalah setanding dengan Glibenklamid (1mg/kg b), di mana paras glukosa dalam darah dipulihkan secara ketara (ANOVA, $p<0.05$) dalam masa 60 minit selepas diberi glukosa. Selain itu, pada akhir kajian antidiabetes selama 28 hari, didapati bahawa aktiviti antihiperglisemia oleh kombinasi dwiherba pada kepekatan 250 mg/kg juga setanding dengan ubat-ubatan kawalan positif, iaitu Glibenklamid (1 mg/kg), Metformin (50 mg/kg) dan Sitagliptin (10 mg/kg), kerana, di bawah rawatan ini, keadaan hiperglisemia tikus teraruh diabetes tidak bertambah buruk atau meningkat sepanjang kajian yang berlangsung selama empat minggu. Kehadiran pelbagai jenis sebatian polifenol seperti asid kafeik dan taraxacin dalam *T. officinale* serta charantin dan polipeptida-p dalam *M. charantia* telah menyumbang kepada pelbagai sifat antidiabetik yang ditunjukkan oleh kedua-dua herba ini. Ini membuktikan bahawa aktiviti antidiabetik oleh kombinasi dwiherba adalah lebih baik berbanding ekstrak etanol tunggal *T. officinale* dan *M. charantia*, disebabkan oleh aktiviti sinergi kedua-dua herba ini. Oleh yang demikian, kombinasi dwiherba ini terbukti berpotensi untuk dikembangkan seterusnya menjadi rawatan herba yang selamat dan kurang bertoksik bagi menangani penyakit Diabetes mellitus Jenis 2.

ACKNOWLEDGEMENTS

First and foremost, I would like to take this opportunity to express my gratitude to the Almighty, Divine Lord for gracing me with courage, strength, persistence and knowledge to complete this study. None of this would have been possible without His will and blessings.

My deepest heartfelt gratitude to my dearest Supervisor, Dr Meenakshii Nallappan for her utmost patience, dedication and love in guiding me to complete this study. She is a great pillar of support and a true friend who always stands by me all along.

I would also like to extend my humble thanks to my committee members, Dr. Nur Kartinee Kassim and Dr. Shamarina Shohaimi for sharing their knowledge and expertise as well as equipping me with valuable ideas and support in successfully completing this study.

I would also like to extend my gratitude to Dr Tee Thiam Tsui and Dr Cheah Yew Hoong from ZACH Biotech Depot Sdn. Bhd. for their generosity in aiding this project financially as well as providing incomparable ideas, comments and insights throughout the study. I am ever thankful for the selfless help rendered by them in the times of need.

I also take this chance to thank all my labmates, Oon Seok Fang, the late Saknah, Ng Rou Chian, Lim Pei Cee, Siti Fara Najua binti Mohd Nasir, Tan Dai Chuan and Alexandra Quek as well as my friends Sujithra Devi a/p Arunagiri Theva, Banulata a/p Gopalsamy and Pravinaa a/p Sooryanarayanan for always being there for me whenever I needed any assistance, motivation, guidance and support.

Last but never the least, my loving family, Amma, Appa, Tata, Patti, Uncles, Aunties and Cousins who stood by me with never-ending faith and patience. Their love and support motivated me to never give up hope and complete what I have started.

Never forgetting, my sincere thanks to the Ministry of Education Malaysia for their financial support through MyBrain15.

I certify that a Thesis Examination Committee has met on (date of viva voce) to conduct the final examination of (student's name) on his (her) thesis entitled ("Title of Thesis") 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 (insert the name of relevant degree).

Members of the Thesis Examination Committee were as follows:

Name of Chairperson, PhD
Title (e.g., Professor/Associate Professor/Ir; omit if irrelevant)
Name of Faculty
Universiti Putra Malaysia
(Chairman)

Name of Examiner 1, PhD
Title (e.g., Professor/Associate Professor/Ir; omit if irrelevant)
Name of Faculty
Universiti Putra Malaysia
(Internal Examiner)

Name of Examiner 2, PhD
Title (e.g., Professor/Associate Professor/Ir; omit if irrelevant)
Name of Faculty
Universiti Putra Malaysia
(Internal Examiner)

Name of External Examiner, PhD
Title (e.g., Professor/Associate Professor/Ir; omit if irrelevant)
Name of Department and/or Faculty
Name of Organisation (University/Institute)
Country
(External Examiner)

_____
Prof. Ts. Dr. Zuriati Ahmad Zukarnain, PhD)
Professor and Deputy Dean
School of Graduate Studies
Universiti Putra Malaysia

Date:

This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Doctor of Philosophy. The members of the Supervisory Committee were as follows:

Meenakshii a/p Nallappan, PhD
Senior Lecturer
Faculty of Science
Universiti Putra Malaysia
(Chairman)

Nur Kartinee binti Kassim, PhD
Senior Lecturer
Faculty of Science
Universiti Putra Malaysia
(Member)

Shamarina binti Shohaimi, PhD
Associate Professor
Faculty of Science
Universiti Putra Malaysia
(Member)

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

Date: 14 October 2021

Declaration by graduate student

I hereby confirm that:

- this thesis is my original work;
- quotations, illustrations and citations have been duly referenced;
- this thesis has not been submitted previously or concurrently for any other degree at any other institutions;
- intellectual property from the thesis and copyright of thesis are fully-owned by Universiti Putra Malaysia, as according to the Universiti Putra Malaysia (Research) Rules 2012;
- written permission must be obtained from supervisor and the office of Deputy Vice-Chancellor (Research and Innovation) before thesis is published (in the form of written, printed or in electronic form) including books, journals, modules, proceedings, popular writings, seminar papers, manuscripts, posters, reports, lecture notes, learning modules or any other materials as stated in the Universiti Putra Malaysia (Research) Rules 2012;
- there is no plagiarism or data falsification/fabrication in the thesis, and scholarly integrity is upheld as according to the Universiti Putra Malaysia (Graduate Studies) Rules 2003 (Revision 2012-2013) and the Universiti Putra Malaysia (Research) Rules 2012. The thesis has undergone plagiarism detection software.

Signature: _____ Date: _____

Name and Matric No.: Nithiyaa a/p Perumal (GS38216)

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS

2-NBDG	2-(N-(7-Nitrobenz-2-oxa-1,3-diazol-4-yl) Amino)-2-Deoxyglucose
Abs	Absorbance
ADA	American Diabetes Association
AlCl3	Aluminium trichloride
AMC	Gly-Pro-Aminomethylcoumarin
AMPK	Adenosine monophosphate- activated protein kinase
ANOVA	Analysis of variance
ARM	Ames Reflectance Meter
ATCC	American Type Culture Collection
b.w	Body weight
BC	Before Christ
CAMs	Complementary and alternative medicines
CG	cytosine guanine
COMeT	Comparative Medicine and Technology Unit
CpG	cytosine guanine sites
DM	Diabetes mellitus
DMEM	Dulbecco's Modified Eagle's Medium
DMSO	Dimethylsulfoxide
DNA	Deoxyribonucleic acid
DPPH	2,2-diphenyl-1-picrylhydrazyl
DPP-4	dipeptidyl peptidase IV
FBG	Fasting blood glucose

FBS	Fetal bovine serum
FDA	Food and Drug Administration
FPG	Fasting Plasma Glucose
GIP	Glucose-dependent insulinotropic polypeptide
GLP-1	Glucagon-like peptide
GLUT4	Glucose Transporter type 4
HbA1c	Hemoglobin A1c
HDL	High-density lipoprotein
HIV	Human immunodeficiency viruses
IACUC	Institutional Animal Care and Use Committee
IC50	Half maximal inhibitory concentration
IDDM	Insulin-dependent diabetes mellitus
IDF	International Diabetes Federation
IL-6	Interleukin-6
IP	Intraperitoneal
K-ATP	Potassium sensitive-adenosine triphosphate
LDL	Low-density lipoprotein
M	Molar
MC/A	Acetone extraction of *M. charantia*
MC/ChCL3	Chloroform extraction of *M. charantia*
MC/EA	Ethyl acetate extraction of *M. charantia*
MC/ETOH	Ethanol extraction of *M. charantia*
MC/H2O	Water extraction of *M. charantia*
MC/PE	Petroleum ether extraction of *M. charantia*

mRNA	Messenger Ribonucleic acid
NA	Nicotinamide
NIDDM	Non-insulin dependent diabetes mellitus
OECD	Organization for Economic Co-operation and Development
OGTT	Oral Glucose Tolerance Test
PBS	Phosphate buffer saline
PNP	4-Nitrophenol
PNPG	4-nitrophenyl-α-D-glucopyranoside
PPAR-γ	Peroxisome proliferator activated receptor
RNA	Ribonucleic acid
ROS	Reactive oxygen species
SGLT2	Sodium-glucose cotransporter-2
SRB	Sulphorhodamine B
STZ	Streptozotocin
T2DM	Type 2 Diabetes mellitus
TCA	Trichloroacetic acid
TFC	Total flavonoid content
TGR5	G protein-coupled receptor
TNF-α	Tumour necrosis factor alpha
TO/A	Acetone extraction of *T. officinale*
TO/ChCL3	Chloroform extraction of *T. officinale*
TO/EA	Ethyl acetate extraction of *T. officinale*
TO/ETOH	Ethanol extraction of *T. officinale*
TO/H2O	Water extraction of *T. officinale*

TO/PE	Petroleum ether extraction of *T. officinale*
TPC	Total phenolic content
WHO	World Health Organization

CHAPTER 1

INTRODUCTION

1.1 Background of Study

Diabetes mellitus (DM) is a metabolic disorder characterized by abnormally high levels of blood glucose (Ching June et al., 2012). Although not contagious, this disease is regarded as one of the leading causes of death besides causing other health complications such as heart disease, high blood pressure, stroke and kidney failure (Nain et al., 2012). There are two major types of DM, first is the inability of the beta cells in the pancreatic to secrete insulin efficiently in response to raised blood glucose level in the system and the second type refers to resistance towards insulin, which points to the inefficiency of the liver, muscle and adipose tissue to respond to insulin secreted by the beta cells (Wang et al., 2007).

In 2019, the International Diabetes Federation (IDF) recorded that 463 million people around the world suffered with DM and by 2045, this figure was speculated to rise to 700 million. Among the Asian countries, Malaysia a developing country with a total population of 32.7 million, which accounts just 0.4% of the entire world population, regrettably hold the highest record of DM sufferers, surpassing China and India. Apart from deteriorating a person's health, DM is also known to be a very expensive disease and a huge burden to the country's economics, where the medical expenditure of a person with diabetes is twice than that of a non-diabetic person (Petersen, 2003).

1.2 Problem Statement

In line with the persistent increase of DM cases around the world, numerous conventional antidiabetic drugs are available over the counter and the invention of latest drugs are continuously flooding in. Antidiabetic medications are prescribed according to the types of DM. Treatment to Type 1 DM is restricted to the use of various insulin analogues via subcutaneous injection to maintain a near normoglycemic condition in patients (Jacobsen et al., 2009). As for Type 2 DM, various classes of oral diabetic drugs such as biguanides, sulfonylurea derivatives, incretin-based therapies such as dipeptidyl peptidase 4 (DPP-4) inhibitors as well as alpha glucosidase inhibitors are prescribed by physicians (Ahmed et al., 2014). Some of these classes of drugs works in complementary to each other hence they are usually taken in combination to successfully lower the blood glucose level in patients with Type 2 DM (Blonde & San Juan, 2012).

Although these drugs are largely used to treat DM, they are used with caution owing to the toxicity and side effects that render reduced renal function in patients (Ioannidis, 2014). Other side effects of these drugs are hypoglycemia, lactic acidosis, flatulence, diarrhea, hepatic disease, heart failure and pancreatitis to name a few (Babiker & Dubayee, 2017; Lankatillake et al., 2019). Due to the rising risk of consuming conventional diabetic drugs, the need for a safer and cost effective alternative remedy, preferably from the dietary sources and especially plant based, are highly sought after (Salehi et al., 2019).

1.3 Justification of Study

Owing to the need to discover an unconventional, plant-based therapy to treat DM, various researches in the field of ethnobotany are continuously being conducted. The result of these studies has led to the uncovering of numerous plants with antidiabetic properties. For instance, *Opuntia streptacantha* Lem (buah pir berduri), *Trigonella foenum graecum* L. (halba), *Taraxacum officinale* (L.) Weber ex F.H.Wigg (rumpun Jombang), *Momordica charantia* L. (peria katak), *Ficus benghalensis* L. (Pokok Ara), *Polygala senega* L. (akar ular), *Gymnema sylvestre* (Retz.) R.Br. ex Sm. (tumbuhan gurmar), *Allium sativum* L. (bawang putih), *Aloe vera* (L.) Burm.f. (lidah buaya), *Azadirachta indica* A.Juss. (pokok mambu) and *Citrullus colocynthis* (L.) Schrad. (timun pahit) are several plants identified to display hypoglycemic properties (Bnouham et al., 2006; Grover et al., 2002; Petchi et al., 2014; Salehi et al., 2019).

The discovery of numerous herbal plants with various antidiabetic mechanisms have encouraged researches to produce various dual herbal formulations to treat DM, a multifactorial disease. Compared to single extracts, dual herbal formulation has been proven to have better and long lasting therapeutic potential (Petchi et al., 2014). In this present study, the antidiabetic potential of dual herbal combination of *Taraxacum officinale* (L.) Weber ex F.H.Wigg and *Momordica charantia* L. extracts was studied.

According to previous studies, both *T. officinale* and *M. charantia* have been known to contain crucial antidiabetic properties (Ahmad et al., 2009; Goyal, 2015; Grover & Yadav, 2004; Koupy et al., 2015; Schutz, Carle, et al., 2006; Singh et al., 2011; Yarnell & Abascal, 2009). *T. officinale* or better known as dandelions have been used as a phytomedicine for its choleretic, diuretic, anti-rheumatic and anti-inflammatory properties (Hu and Kitts, 2005). Previous study by Tsuda et al. (2012) showed that chlorogenic acid and caffeic acid found in *T. officinale* have been explored for their antihyperglycemic properties, where caffeic acid in particular has been reported to decrease blood glucose in test animals. In another study done by Ding et al. (2010), luteolin has been found to increase insulin action, besides decreasing the expression of a particular gene responsible for inflammation of cytokines, as well as inducing the gene and

protein expression Glucose Transporter type 4 (GLUT4) which assist glucose uptake by the cells.

M. charantia or bitter melon on the other hand is most widely used in countries such as China, India, Asia, and Africa, as a customary medication to treat diabetes and is known as one of the most promising alternative medicines for this disease (Ahmad et al., 2009; Kumar et al., 2009; Roffey et al., 2007). Besides treating diabetes, *M. charantia* is also used extensively as a medicinal herb for treating anti-HIV, anti-ulcer, anti-inflammatory, anti-leukemic, anti-microbial, and anti-tumor (Kumar et al., 2009). Certain compounds extracted from *M. charantia* such as charantin, oleanolic acid, oleanolic acid 3-O-glucuronide, polypeptide-p, momordin and 3-O-monodesmoside have shown hypoglycemic activity (Grover and Yadav, 2004). The juice of *M. charantia* has also shown the ability to recover partially destroyed pancreatic cells in diabetic rats besides stimulating insulin secretion from the pancreas and bring forth glucose uptake in the liver.

Herbal combination of two or more plant extracts were found to have more promising effects on diseases compared to single herb (Aslam et al., 2016). The concept of dual herbal combination has been very well received worldwide due to its potential interaction effects of various ailments Hence, this study aims to explore the combined antidiabetic activities of potential extracts from both *T. officinale* and *M. charantia*, which would be instrumental in developing this dual herbal combination into a pharmaceutical drug to treat Type 2 DM.

Having proven to contain numerous essential antidiabetic compounds, *T. officinale* and *M. charantia* are worthy choices of plants to study their combined effect on anti-hyperglycemic properties so as to meet the demands for an alternative treatment for DM.

1.4 Objectives of the Study

To evaluate the efficacy and antidiabetic action of combined dual herbal formulation from *T. officinale* and *M. charantia*.
The objectives of this study are:

1. To determine the 2,2-diphenyl-1-picrylhydrazyl (DPPH) scavenging activity, total phenolic content (TPC), and total flavonoid content (TFC) of *T. officinale* and *M. charantia* crude extracts

2. To examine the effect of *T. officinale* and *M. charantia* crude extracts on glucose uptake in L6 muscle cells using a cell-based assay

3. To examine the effect of *T. officinale* and *M. charantia* crude extracts in inhibiting the dipeptidyl peptidase-IV (DPP-4) enzyme via a non-cell-based enzyme-substrate reaction assay

4. To examine the effect of *T. officinale* and *M. charantia* crude extracts in inhibiting the α-amylase and α-glucosidase enzyme via a non-cell-based enzyme-substrate reaction assay

5. To explore the combined effects of *T. officinale* and *M. charantia* most potent crude extract *in vitro* antidiabetic assays (glucose uptake in L6 muscle cell and the inhibition of DPP-4, α-amylase and α-glucosidase enzymes) and *in vivo* streptozotocin-nicotinamide (STZ-NA) induced diabetic model rats.

1.5 Hypotheses of Study

The *T. officinale* and *M. charantia* crude extracts exhibits DPPH scavenging properties, and possess phenolic and flavonoid compounds.

The *T. officinale* and *M. charantia* crude extracts show glucose uptake activity in L6 muscle cells

The *T. officinale* and *M. charantia* crude extracts exhibit DPP-4 inhibitory activity

The *T. officinale* and *M. charantia* crude extracts inhibit the α-glucosidase and α-amylase enzyme

The dual herbal combination of *T. officinale* and *M. charantia* active crude extracts exhibits antidiabetes activity in *in vitro* antidiabetic assays and *in vivo* STZ-NA induced diabetic model rats.

REFERENCES

Abdul Razak, M. F. B., Yong, P. K., Shah, Z. M., Abdullah, L. C., Yee, S. S., & Yaw, I. T. C. S. (2012). The Effects of varying solvent polarity on extraction yield of Orthosiphon stamineus leaves. *Journal of Applied Sciences*, *12*(11), 1207–1210. https://doi.org/10.3923/jas.2012.1207.1210

Abdullah, N., Attia, J., Oldmeadow, C., Scott, R. J., & Holliday, E. G. (2014). The architecture of risk for type 2 diabetes: Understanding asia in the context of global findings. In *International Journal of Endocrinology* (Vol. 2014). Hindawi Publishing Corporation. https://doi.org/10.1155/2014/593982

Abdullah, N, & Kasim, K. F. (2017). In-Vitro Antidiabetic Activity of Clinacanthus nutans Extracts. *International Journal of Pharmacognosy and Phytochemical Research*, *9*(6), 846–852.

Abdullah, Noraidatulakma, Abdul Murad, N., Attia, J., Oldmeadow, C., Kamaruddin, M., Abd Jalal, N., Ismail, N., Jamal, R., Scott, R., Holliday, E., Abdullah, N., Abdul Murad, N. A., Attia, J., Oldmeadow, C., Kamaruddin, M. A., Abd Jalal, N., Ismail, N., Jamal, R., Scott, R. J., & Holliday, E. G. (2018). Differing Contributions of Classical Risk Factors to Type 2 Diabetes in Multi-Ethnic Malaysian Populations. *International Journal of Environmental Research and Public Health*, *15*(12), 2813. https://doi.org/10.3390/ijerph15122813

Agarwal, A., Jadhav, P. ., & Deshmukh, Y. . (2014). Prescribing pattern and efficacy of anti-diabetic drugs in maintaining optimal glycemic levels in diabetic patients. *Journal of Basic and Clinical Pharmacy*, *5*(3), 79. https://doi.org/10.4103/0976-0105.139731

Ahmad, M., Qureshi, R., Arshad, M., Khan, M. A., & Zafar, M. (2009). Traditional herbal remedies used for the treatment of diabetes from district attock (Pakistan). *Pakistan Journal of Botany*, *41*(6), 2777–2782.

Ahmed, A. M. (2002). History of diabetes mellitus. *Saudi Medical Journal*, *23*(4), 373–378. https://doi.org/10.2337/diab.13.5.542b

Ahmed, S. ., Ali, M. ., Laila, T. ., Begum, H. ., & Ali, T. M. . (2014). An update on pharmacotherapy for type 2 diabetes. In *Malta Medical Journal* (Vol. 26, Issue 4, pp. 29–38). University of Malta. https://doi.org/10.3329/kyamcj.v3i1.13661

AL-Zuaidy, M. H., Ismail, A., Mohamed, S., Razis, A. F. A., Mumtaz, M. W., & Hamid, A. A. (2018). Antioxidant effect, glucose uptake activity in cell lines and cytotoxic potential of Melicope lunu-ankenda leaf extract. *Journal of Herbal Medicine*, *14*, 55–60. https://doi.org/10.1016/j.hermed.2018.06.002

Ali, H., Anwar, M., Ahmad, T., & Chand, N. (2006). Diabetes Mellitus from Antiquity to Present Scenario and Contribution of Greco-Arab Physicians. *Journal of the International Society for the History of Islamic Medicine*,

5(10), 46–50.

Alqahtani, A. S., Hidayathulla, S., Rehman, M. T., Elgamal, A. A., Al-Massarani, S., Razmovski-Naumovski, V., Alqahtani, M. S., El Dib, R. A., & Alajmi, M. F. (2020). Alpha-amylase and alpha-glucosidase enzyme inhibition and antioxidant potential of 3-oxolupenal and katononic acid isolated from Nuxia oppositifolia. *Biomolecules*, *10*(1). https://doi.org/10.3390/biom10010061

Ambastha, L., & Kaushik, S. (2011). *Ip Review : Blood Glucose Meter a White Paper*.

America Diabetes Association. (2009). Diagnosis and classification of diabetes mellitus. *Diabetes Care*, *32*(1). https://doi.org/10.2337/dc09-S062

American Diabetes Association. (2003). Standards of medical care for patients with diabetes mellitus. *Diabetes Care*, *26*(1), 33–50. https://doi.org/10.2337/diacare.25.1.213

American Diabetes Association. (2012). Standards of medical care in diabetes - 2012. *Diabetes Care*, *35*(SUPPL. 1). https://doi.org/10.2337/dc12-s011

American Diabetes Association. (2019). 9. Pharmacologic approaches to glycemic treatment: Standards of medical care in diabetesd2019. *Diabetes Care*, *42*(1), S90–S102. https://doi.org/10.2337/dc19-S009

American Diabetes Association. (2020). Introduction : Standards of Medical Care in Diabetes d 2019. *Diabetes Care*, *43*(1), S1–S2.

Amin Mir, M., Sawhney, S., & Jassal, M. (2013). 2013 Wudpecker Journals Qualitative and quantitative analysis of phytochemicals of Taraxacum officinale. *Wudpecker Journal of Pharmacy and Pharmocology*, *2*(1), 1–005. https://pdfs.semanticscholar.org/fb65/97543d933256cbe8db76f99cef94e426860c.pdf

Amin Mir, M., Sawhney, S. S., & S Jassal, M. M. (2015). In-vitro antidiabetic studies of various extracts of Taraxacum officinale. *~ 61 ~ The Pharma Innovation Journal*, *4*(1), 61–66. www.thepharmajournal.com

Amira, K., Aminah, A., & Zuhair, A. (2013). Evaluation of bitter melon (Momordica charantia) extract administration in the antioxidant and free radical scavenging activities of plasma and liver in male rat. *International Food Research Journal*, *20*(1), 319–323.

Anilakumar, K. ., Kumar, G. ., & Ilaiyaraja, N. (2015). Nutritional, Pharmacological and Medicinal Properties of Momordica Charantia. *International Journal of Nutrition and Food Sciences*, *4*(1), 75. https://doi.org/10.11648/j.ijnfs.20150401.21

Anjamma, M., & Lakshmi Bhavani, N. (2017). GC-MS Analysis of Momordica charantia and Momordica dioica Fruit and Root Methanolic Extracts.

International Journal of Pharmacognosy and Phytochemical Research, *9*(6), 808–813. https://doi.org/10.25258/phyto.v9i6.8183

Aremu, M., Waziri, A., Faleye, F., Magomya, A., & Okpaegbe, U. (2019). Lipids profile of bitter melon (Momordica charantia L .) fruit and ebony (Diospyros mespiliformis Hochst ex A. DC .) tree fruit pulp. *Bangladesh Journal of Scientific and Industrial Research*, *54*(4), 367–374. https://doi.org/10.3329/bjsir.v54i4.44571

Asif, M. (2014). The prevention and control the type-2 diabetes by changing lifestyle and dietary pattern. *Journal of Education and Health Promotion*, *3*(1), 1. https://doi.org/10.4103/2277-9531.127541

Aslam, M. S., Ahmad, M. S., Mamat, A. S., Ahmad, M. Z., & Salam, F. (2016). An update review on polyherbal formulation: A global perspective. *Systematic Reviews in Pharmacy*, *7*(1), 35–41. https://doi.org/10.5530/srp.2016.7.5

Avila, J. A. D., García, J. R., Aguilar, G. A. G., & De La Rosa, L. A. (2017). The antidiabetic mechanisms of polyphenols related to increased glucagon-like peptide-1 (GLP1) and insulin signaling. *Molecules*, *22*(6), 1–16. https://doi.org/10.3390/molecules22060903

Babiker, A., & Dubayee, M. (2017). Anti-diabetic medications: How to make a choice? *Sudanese Journal of Paediatrics*, *17*(2), 11–20. https://doi.org/10.24911/sjp.2017.2.12

Baek, H. J., Jeong, Y. J., Kwon, J. E., Ra, J. S., Lee, S. R., & Kang, S. C. (2018). Antihyperglycemic and Antilipidemic Effects of the Ethanol Extract Mixture of Ligularia fischeri and Momordica charantia in Type II Diabetes-Mimicking Mice. *Evidence-Based Complementary and Alternative Medicine*, *2018*. https://doi.org/10.1155/2018/3468040

Baggio, L. L., & Drucker, D. . (2007). Biology of Incretins: GLP-1 and GIP. *Gastroenterology*, *132*(6), 2131–2157. https://doi.org/10.1053/j.gastro.2007.03.054

Bailey, C. J. (2017). Metformin: historical overview. *Diabetologia*, *60*(9), 1566–1576. https://doi.org/10.1007/s00125-017-4318-z

Bajaj, S., & Khan, A. (2014). Mini Review Antioxidants and diabetes. *Indian Journal of Endocrinology and Metabolism*, *16*(Suppl 2), S267-71. https://doi.org/10.4103/2230-8210.104057

Balbi, M. E., Tonin, F. S., Mendes, A. M., Borba, H. H., Wiens, A., Fernandez-Llimos, F., & Pontarolo, R. (2018). Antioxidant effects of vitamins in type 2 diabetes: A meta-analysis of randomized controlled trials. *Diabetology and Metabolic Syndrome*, *10*(1), 1–12. https://doi.org/10.1186/s13098-018-0318-5

Ballagi-Pordany, G., Koszeghy, A., Koltai, M. ., Aranyi, Z., & Pogatsa, G. (1990). Divergent cardiac effects of the first and second generation hypoglycemic

sulfonylurea compounds. *Diabetes Research and Clinical Practice*, *8*(2), 109–114. https://doi.org/10.1016/0168-8227(90)90020-T

Bansal, A., & Pinney, S. E. (2017). DNA methylation and its role in the pathogenesis of diabetes. *Pediatric Diabetes*, *18*(3), 167–177. https://doi.org/10.1111/pedi.12521

Barchan, A., Bakkali, M., Arakrak, A., Pagán, R., & Laglaoui, A. (2014). The effects of solvents polarity on the phenolic contents and antioxidant activity of three Mentha species extracts. *International Journal of Current Microbiology and Applied Sciences*, *3*(11), 399–412.

Barrett, A. H., Farhadi, N. F., & Smith, T. J. (2018). Slowing starch digestion and inhibiting digestive enzyme activity using plant flavanols/tannins— A review of efficacy and mechanisms. *LWT - Food Science and Technology*, *87*, 394–399. https://doi.org/10.1016/j.lwt.2017.09.002

Baynes, J. W., & Thorpe, S. R. (1996). The role of oxidative stress in diabetic complications. *Current Opinion in Endocrinology and Diabetes*, *3*(4), 277–284. https://doi.org/10.1097/00060793-199608000-00001

Bays, H., Mandarino, L., & DeFronzo, R. A. (2004). Role of the Adipocyte, Free Fatty Acids, and Ectopic Fat in Pathogenesis of Type 2 Diabetes Mellitus: Peroxisomal Proliferator-Activated Receptor Agonists Provide a Rational Therapeutic Approach. *Journal of Clinical Endocrinology and Metabolism*, *89*(2), 463–478. https://doi.org/10.1210/jc.2003-030723

Bhuiyan, M. A. R., & Hoque, M. Z. (2010). Free radical scavenging activities of Zizyphus mauritiana. *Electronic Journal of Environmental, Agricultural and Food Chemistry*, *9*(1), 199–206.

Blainski, A., Lopes, G. C., & De Mello, J. C. P. (2013). Application and analysis of the folin ciocalteu method for the determination of the total phenolic content from limonium brasiliense L. *Molecules*, *18*(6), 6852–6865. https://doi.org/10.3390/molecules18066852

Blonde, L., & San Juan, Z. T. (2012). Fixed-dose combinations for treatment of type 2 diabetes mellitus. *Advances in Therapy*, *29*(1), 1–13. https://doi.org/10.1007/s12325-011-0094-1

Bnouham, M., Ziyyat, A., Mekhfi, H., Tahri, A., & Legssyer, A. (2006). *Medicinal plants with potential antidiabetic activity-A review of ten years of herbal medicine research (1990-2000) Medicinal plants with potential antidiabetic activity - A review of ten years of herbal medicine research (1990-2000)*. *April*. https://doi.org/10.1159/000497588

Bosenberg, L. H., & Van Zyl, D. G. (2008). The mechanism of action of oral antidiabetic drugs: A review of recent literature. *Journal of Endocrinology, Metabolism and Diabetes of South Africa*, *13*(3), 80–89. https://doi.org/10.1080/22201009.2008.10872177

Cani, P. D., Neyrinck, A. M., Maton, N., & Delzenne, N. M. (2005). Oligofructose

promotes satiety in rats fed a high-fat diet: Involvement of glucagon-like peptide. *Obesity Research*, *13*(6), 1000–1007. https://doi.org/10.1038/oby.2005.117

Ceriello, A. (2000). Oxidative stress and glycemic regulation. *Metabolism: Clinical and Experimental*, *49*(2 SUPPL. 1), 27–29. https://doi.org/10.1016/S0026-0495(00)80082-7

Chaubey, P., Suvarna, V., Sangave, P. C., & Singh, A. K. (2019). Nutritional Management of Diabetes—A Critical Review. In *Bioactive Food as Dietary Interventions for Diabetes* (2nd ed.). Elsevier Inc. https://doi.org/10.1016/b978-0-12-813822-9.00019-9

Chaudhury, A., Duvoor, C., Reddy Dendi, V. S., Kraleti, S., Chada, A., Ravilla, R., Marco, A., Shekhawat, N. S., Montales, M. T., Kuriakose, K., Sasapu, A., Beebe, A., Patil, N., Musham, C. K., Lohani, G. P., & Mirza, W. (2017). Clinical Review of Antidiabetic Drugs: Implications for Type 2 Diabetes Mellitus Management. *Frontiers in Endocrinology*, *8*(January). https://doi.org/10.3389/fendo.2017.00006

Cheah, Y. H., Nordin, F. J., Tee, T. T., Azimahtol, H. L. P., Abdullah, N. R., & Ismail, Z. (2008). Antiproliferative property and apoptotic effect of xanthorrhizol on MDA-MB-231 breast cancer cells. *Anticancer Research*, *28*(6A), 3677–3689. http://www.ncbi.nlm.nih.gov/pubmed/19189649

Chen, J. ., Chiu, M. ., Nie, R. ., Cordell, G. ., & Qiu, S. . (2005). Cucurbitacins and Cucurbitane Glycosides: Structures and Biological Activities. *Organic Chemistry*, *22*(5), 386–399.

Chen, R., Ovbiagele, B., & Feng, W. (2016). Diabetes and Stroke: Epidemiology, Pathophysiology, Pharmaceuticals and Outcomes. *The American Journal of Medical Sciences*, *351*(4), 380–386. https://doi.org/10.1016/j.physbeh.2017.03.040

Chew, B. H., Mastura, I., Lee, P. Y., Sri Wahyu, T., Cheong, A. T., & Zaiton, A. (2011). Ethnic Differences in Glycaemic Control and Complications: The Adult Diabetes Control and Management (ADCM), Malaysia. *Medical Journal of Malaysia*, *66*(3), 244–248.

Ching June, C., Hui Wen, L., Abdullah Sani, H., Latip, J., Azlan Gansau, J., Ping Chin, L., Embi, N., & Mohd Sidek, H. (2012). Hypoglycemic Effects of Gynura procumbens Fractions on Streptozotocin-induced Diabetic Rats involved Phosphorylation of GSK3β (Ser-9) in Liver (Kesan Hipoglisemik Fraksi Gynura procumbens di dalam Tikus Diabetes Aruhan-Streptozotocin Melibatkan Pemfosfatan GSK3β (Ser-9) Hepar). In *Sains Malaysiana* (Vol. 41, Issue 8).

Cho, S.-Y., Park, J.-Y., Park, E.-M., Choi, M.-S., Lee, M.-K., Jeon, S.-M., Jang, M. K., Kim, M.-J., & Park, Y. B. (2002). Alternation of hepatic antioxidant enzyme activities and lipid profile in streptozotocin-induced diabetic rats by supplementation of dandelion water extract. *Clinica Chimica Acta*, *317*(1–

2), 109–117. https://doi.org/10.1016/S0009-8981(01)00762-8

Clarke, S. F., & Foster, J. R. (2012). A history of blood glucose meters and their role in self-monitoring of diabetes mellitus. *British Journal of Biomedical Science*, *69*(2), 83–93. https://doi.org/10.1080/09674845.2012.12002443

Cornell, S. (2015). Continual evolution of type 2 diabetes: An update on pathophysiology and emerging treatment options. *Therapeutics and Clinical Risk Management*, *11*, 621–632. https://doi.org/10.2147/TCRM.S67387

Costa, J. G. M., Nascimento, E. M. M., Campos, A. R., & Rodrigues, F. F. G. (2010). Antibacterial activity of Momordica charantia (Curcubitaceae) extracts and fractions. *Journal of Basic and Clinical Pharmacy*, *2*(1), 45–51.

Cummings, E., Hundal, H. S., Wackerhage, H., Hope, M., Belle, M., Adeghate, E., & Singh, J. (2004). Momordica charantia fruit juice stimulates glucose and amino acid uptakes in L6 myotubes. *Molecular and Cellular Biochemistry*, *261*(1), 99–104. https://doi.org/10.1023/B:MCBI.0000028743.75669.ab

Davison, J. . (1947). History of the Measurement of Glucose. *Medical History*, *18*(2), 194–197.

Day, C., Cartwright, T., Provost, J., & Bailey, C. J. (1990). Hypoglycaemic effect of Momordica charantia extracts. *Planta Medica*, *56*(5), 426–429. https://doi.org/10.1055/s-2006-961003

Day, Caroline. (2001). The rising tide of type 2 diabetes. *The British Journal of Diabetes & Vascular Disease*, *1*(1), 37–43. https://doi.org/10.1177/14746514010010010601

de Bairacli-Levy, J. (1991). *Herbal Handbook for Farm and Stable*. Faber & Faber.

Delzenne, N. M., Cani, P. D., & Neyrinck, A. M. (2007). Modulation of Glucagon-like Peptide 1 and Energy Metabolism by Inulin and Oligofructose: Experimental Data. *The Journal of Nutrition*, *137*(11), 2547S-2551S. https://doi.org/10.1093/jn/137.11.2547s

Dhanani, T., Shah, S., Gajbhiye, N. A., & Kumar, S. (2017). *Effect of extraction methods on yield, phytochemical constituents and antioxidant activity of Withania somnifera*. https://doi.org/10.1016/j.arabjc.2013.02.015

Díaz, K., Espinoza, L., Madrid, A., Pizarro, L., & Chamy, R. (2018). Isolation and Identification of Compounds from Bioactive Extracts of Taraxacum officinale Weber ex F. H. Wigg. (Dandelion) as a Potential Source of Antibacterial Agents. *Evidence-Based Complementary and Alternative Medicine : ECAM*, *2018*. https://doi.org/10.1155/2018/2706417

Dicker, D. (2011). DPP-4 inhibitors: impact on glycemic control and

cardiovascular risk factors. *Diabetes Care*, *34 Suppl 2*(Suppl 2), S276-8. https://doi.org/10.2337/dc11-s229

Ding, L., Jin, D., & Chen, X. (2010). Luteolin enhances insulin sensitivity via activation of PPARΓ transcriptional activity in adipocytes. *Journal of Nutritional Biochemistry*, *21*(10), 941–947. https://doi.org/10.1016/j.jnutbio.2009.07.009

Do, Q. D., Angkawijaya, E., Tran-Nguyen, P. L., Huynh, L. H., Soetaredjo, F. E., Ismadji, S., & Ju, Y.-H. (2014). *Effect of extraction solvent on total phenol content, total flavonoid content, and antioxidant activity of Limnophila aromatica*. https://doi.org/10.1016/j.jfda.2013.11.001

Drucker, D. J., & Nauck, M. A. (2006). The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. *Lancet*, *368*(9548), 1696–1705. https://doi.org/10.1016/S0140-6736(06)69705-5

Eahamban, K., & Antonisamy, J. M. (2012). Preliminary Phytochemical, UV-VIS, HPLC and Anti-bacterial Studies on Gracilaria corticata J. Ag. *Asian Pacific Journal of Tropical Biomedicine*, *2*(2 SUPPL.), S568–S574. https://doi.org/10.1016/S2221-1691(12)60275-5

Ekayanti, M., Sauriasari, R., & Elya, B. (2018). Dipeptidyl peptidase IV inhibitory activity of fraction from white tea ethanolic extract (Camellia sinensis (L.) Kuntze) ex vivo. *Pharmacognosy Journal*, *10*(1), 190–193. https://doi.org/10.5530/pj.2018.1.32

Eknoyan, G., & Nagy, J. (2005). A history of diabetes mellitus or how a disease of the kidneys evolved into a kidney disease. *Advances in Chronic Kidney Disease*, *12*(2), 223–229. https://doi.org/10.1053/j.ackd.2005.01.002

Ekor, M. (2014). The growing use of herbal medicines: Issues relating to adverse reactions and challenges in monitoring safety. *Frontiers in Neurology*, *4 JAN*(January), 1–10. https://doi.org/10.3389/fphar.2013.00177

Eldor, R., & Raz, I. (2012). Diabetes therapy-focus on Asia: Second-line therapy debate: Insulin/secretagogues. *Diabetes/Metabolism Research and Reviews*, *28*(SUPPL.2), 85–89. https://doi.org/10.1002/dmrr.2358

Emilien, G., Maloteaux, J. M., & Ponchon, M. (1999). Pharmacological management of diabetes: Recent progress and future perspective in daily drug treatment. *Pharmacology and Therapeutics*, *81*(1), 37–51. https://doi.org/10.1016/S0163-7258(98)00034-5

Escudero, N. L., De Arellano, M. L., Fernández, S., Albarracín, G., & Mucciarelli, S. (2003). Taraxacum officinale as a food source. *Plant Foods for Human Nutrition*, *58*(3), 1–10. https://doi.org/10.1023/B:QUAL.0000040365.90180.b3

Ezebuenyi, M., Jimoh, A., Ambush, E., Nguyen, A., Summers, B., Ozah, M., Obih, J. C., & Obih, P. (2017). Evaluation of Selected Medicinal Herbs for

Antidiabetic Activity Via Alpha-Glucosidase Inhibition. *International Journal of General Medicine and Pharmacy (IJGMP)*, *6*(5), 59–64. http://iaset.us/view_archives.php?year=2017&jtype=2&id=51&details=archives

Fan, J., Johnson, M. H., Lila, M. A., Yousef, G., & de Mejia, E. G. (2013). Berry and Citrus Phenolic Compounds Inhibit Dipeptidyl Peptidase IV: Implications in Diabetes Management. *Evidence-Based Complementary and Alternative Medicine*, *2013*, 1–13. https://doi.org/10.1155/2013/479505

Fatanah, D. N., Abdullah, N., Hashim, N., & Hamid, A. A. (2018). Antioxidant and mutagenic activity of herbal tea prepared from Cosmos caudatus leaves at different maturity stages. *Sains Malaysiana*, *47*(4), 725–730. https://doi.org/10.17576/jsm-2018-4704-10

Fatima, M., Sadeeqa, S., & Nazir, S. U. R. (2018). Metformin and its gastrointestinal problems: A review. *Biomedical Research (India)*, *29*(11), 2285–2289. https://doi.org/10.4066/biomedicalresearch.40-18-526

Fatima, N., & Nayeem, N. (2016). Toxic Effects as a Result of Herbal Medicine Intake. *Toxicology - New Aspects to This Scientific Conundrum*, *October*. https://doi.org/10.5772/64468

Fatima, T., Bashir, O., Naseer, B., & Hussain, S. . (2018). Dandelion: Phytochemistry and clinical potential. *Journal of Medicinal Plants Studies*, *6*(2), 198–202. http://www.plantsjournal.com/archives/2018/vol6issue2/PartC/6-2-42-182.pdf

Feingold, K. R., Evans, J. L., Balkan, B., & Rushakoff, R. (2013). Oral and Injectable (Non-insulin) Pharmacological Agents for Type 2 Diabetes. *Endotext*, *November 2014*. http://www.ncbi.nlm.nih.gov/pubmed/25905364

Feisul, M. ., & Azmi, S. (2013). National Diabetes Registry Report, Volume 1, 2009-2012. In *Ministry of Health Malaysia* (Vol. 1). https://doi.org/10.1021/j100223a011

Filippatos, T. D., Panagiotopoulou, T. V., & Elisaf, M. S. (2014). Adverse Effects of GLP-1 Receptor Agonists. *The Review of Diabetic Studies : RDS*, *11*(3–4), 202–230. https://doi.org/10.1900/RDS.2014.11.202

Fonseca, V. A. (2009). Defining and characterizing the progression of type 2 diabetes. *Diabetes Care*, *32 Suppl 2*. https://doi.org/10.2337/dc09-s301

Free, A. H., Adams, E. C., Kercher, M. L., Free, H. M., & Cook, M. H. (1957). Simple specific test for urine glucose. *Clinical Chemistry*, *3*(3), 163–168. https://doi.org/10.1093/clinchem/3.3.163

García-Carrasco, B., Fernandez-Dacosta, R., Dávalos, A., Ordovás, J., & Rodriguez-Casado, A. (2015). In vitro Hypolipidemic and Antioxidant

Effects of Leaf and Root Extracts of Taraxacum Officinale. *Medical Sciences*, *3*(2), 38–54. https://doi.org/10.3390/medsci3020038

Genuth, S., Alberti, K. G. M. M., Bennett, P., Buse, J., DeFronzo, R., Kahn, R., Kitzmiller, J., Knowler, W. C., Lebovitz, H., Lernmark, A., Nathan, D., Palmer, J., Rizza, R., Saudek, C., Shaw, J., Steffes, M., Stern, M., Tuomilehto, J., & Zimmet, P. (2003). Follow-up Report on the Diagnosis of Diabetes Mellitus. *Diabetes Care*, *26*(11), 3160–3167. https://doi.org/10.2337/diacare.26.11.3160

González-Castejón, M., Visioli, F., & Rodriguez-Casado, A. (2012). Diverse biological activities of dandelion. *Nutrition Reviews*, *70*(9), 534–547. https://doi.org/10.1111/j.1753-4887.2012.00509.x

Goyal, M. (2015). Traditional plants used for the treatment of diabetes mellitus in Sursagar constituency, Jodhpur, Rajasthan - An ethnomedicinal survey. *Journal of Ethnopharmacology*, *174*, 364–368. https://doi.org/10.1016/j.jep.2015.08.047

Grover, J. K., & Yadav, S. P. (2004). Pharmacological actions and potential uses of Momordica charantia: A review. *Journal of Ethnopharmacology*, *93*(1), 123–132. https://doi.org/10.1016/j.jep.2004.03.035

Gunes, H., Alper, M., & Celikoglu, N. (2019). Anticancer effect of the fruit and seed extracts of Momordica charantia L. (Cucurbitaceae) on human cancer cell lines. *Tropical Journal of Pharmaceutical Research*, *18*(10), 2057–2065. https://doi.org/10.4314/tjpr.v18i10.9

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. In *Diabetology and Metabolic Syndrome* (Vol. 9, Issue 1). BioMed Central Ltd. https://doi.org/10.1186/s13098-017-0254-9

Haffner, S. M., Greenberg, A. S., Weston, W. M., Chen, H., Williams, K., & Freed, M. I. (2002). Effect of rosiglitazone treatment on nontraditional markers of cardiovascular disease in patients with type 2 diabetes mellitus. *Circulation*, *106*(6), 679–684. https://doi.org/10.1161/01.CIR.0000025403.20953.23

Handelsman, Y. (2011). Role of bile acid sequestrants in the treatment of type 2 diabetes. *Diabetes Care*, *34*(SUPPL. 2). https://doi.org/10.2337/dc11-s237

Harrigan, R. A., Nathan, M. S., & Beattie, P. (2001). Oral agents for the treatment of type 2 diabetes mellitus: Pharmacology, toxicity, and treatment. *Annals of Emergency Medicine*, *38*(1), 68–78. https://doi.org/10.1067/mem.2001.114314

Hayford, J. T., Weydert, J. A., & Thompson, R. G. (1983). Validity of urine glucose measurements for estimating plasma glucose concentration. *Diabetes Care*, *6*(1), 40–44. https://doi.org/10.2337/diacare.6.1.40

Hendriks, A. M., Schrijnders, D., Kleefstra, N., de Vries, E. G. E., Bilo, H. J. G.,

Jalving, M., & Landman, G. W. D. (2019). Sulfonylurea derivatives and cancer, friend or foe? *European Journal of Pharmacology*, *861*(April), 172598. https://doi.org/10.1016/j.ejphar.2019.172598

Holstein, A., Plaschke, A., & Egberts, E. H. (2001). Lower incidence of severe hypoglycaemia in patients with type 2 diabetes treated with glimepiride versus glibenclamide. *Diabetes/Metabolism Research and Reviews*, *17*(6), 467–473. https://doi.org/10.1002/dmrr.235

Hossain, U., Das, A. K., Ghosh, S., & Sil, P. C. (2020). An overview on the role of bioactive α-glucosidase inhibitors in ameliorating diabetic complications. *Food and Chemical Toxicology*, *145*(September), 111738. https://doi.org/10.1016/j.fct.2020.111738

Houghton, P., Fang, R., Techatanawat, I., Steventon, G., Hylands, P. J., & Lee, C. C. (2007). The sulphorhodamine (SRB) assay and other approaches to testing plant extracts and derived compounds for activities related to reputed anticancer activity. *Methods*, *42*(4), 377–387. https://doi.org/10.1016/J.YMETH.2007.01.003

Hsia, D. S., Grove, O., & Cefalu, W. T. (2017). An Update on SGLT2 Inhibitors for the Treatment of Diabetes Mellitus. *Curr Opin Endocrinol Diabetes Obes*, *24*(1), 73–79. https://doi.org/10.1097/MED.0000000000000311.An

Hu, C., & Kitts, D. D. (2005). Dandelion (Taraxacum officinale) flower extract suppresses both reactive oxygen species and nitric oxide and prevents lipid oxidation in vitro. *Phytomedicine*, *12*(8), 588–597. https://doi.org/10.1016/j.phymed.2003.12.012

Hussin, A. H. (2001). Adverse Effects Of Herbs And Drug-Herbal Interactions. *Malaysian Journal of Pharmacy*, *1*(2), 39–44.

Ingle, P. V., Yin, S. B., Ying, B. J., Leong, B. K., Xin, T. Z., Hwa, L. T., & Mun, L. T. (2018). Current Trends in Pharmacological Treatment of Type II Diabetes Mellitus. *International Journal of Pharmacological Research and Reviews*, *7*(1), 1–15. https://www.researchgate.net/publication/325007874_Current_Trends_in_Pharmacological_Treatment_of_Type_II_Diabetes_Mellitus

Insull, W. (2006). Clinical utility of bile acid sequestrants in the treatment of dyslipidemia: a scientific review. *Southern Medical Journal*, *99*(3), 257–274. https://go.galegroup.com/ps/anonymous?id=GALE%7CA144298829&sid=googleScholar&v=2.1&it=r&linkaccess=abs&issn=00384348&p=AONE&sw=w

Inzucchi, S. E., Bergenstal, R. M., Buse, J. B., Diamant, M., Ferrannini, E., Nauck, M., Peters, A. L., Tsapas, A., Wender, R., & Matthews, D. R. (2012). Management of hyperglycemia in type 2 diabetes: A patient-centered approach. *Diabetes Care*, *35*(6), 1364–1379. https://doi.org/10.2337/dc12-0413

Ioannidis, I. (2014). Diabetes treatment in patients with renal disease: Is the landscape clear enough? *World Journal of Diabetes*, *5*(5), 651. https://doi.org/10.4239/wjd.v5.i5.651

Ivanov, I. G. (2014). Polyphenols content and antioxidant activities of Taraxacum officinale F.H. Wigg (Dandelion) leaves. *International Journal of Pharmacognosy and Phytochemical Research*, *6*(4), 889–893.

Jabbour, S. (2008). Primary care physicians and insulin initiation: Multiple barriers, lack of knowledge or both? *International Journal of Clinical Practice*, *62*(6), 845–847. https://doi.org/10.1111/j.1742-1241.2008.01757.x

Jacobsen, I. B., Henriksen, J. E., Hother-Nielsen, O., Vach, W., & Beck-Nielsen, H. (2009). Evidence-based insulin treatment in type 1 diabetes mellitus. In *Diabetes Research and Clinical Practice* (Vol. 86, Issue 1, pp. 1–10). Elsevier. https://doi.org/10.1016/j.diabres.2009.05.020

Jamal, R., Syed Zakaria, S. Z., Kamaruddin, M. A., Abd Jalal, N., Ismail, N., Mohd Kamil, N., Abdullah, N., Baharudin, N., Hussin, N. H., Othman, H., Mahadi, N. M., Abd Rahman, A. R., Awang, A., Jamil, A. T., Mustafa, A. N., Nuruddin, A. A., Ismail, A., Abd Hamid Karim, A., Nur, A. M., … Ahmad, Z. (2015). Cohort Profile: The Malaysian Cohort (TMC) project: A prospective study of non-communicable diseases in a multi-ethnic population. *International Journal of Epidemiology*, *44*(2), 423–431. https://doi.org/10.1093/ije/dyu089

Janardhan, S., & Sastry, G. (2014). Dipeptidyl Peptidase IV Inhibitors: A New Paradigm in Type 2 Diabetes Treatment. *Current Drug Targets*, *15*(6), 600–621. https://doi.org/10.2174/1389450115666140311102638

Jia, S., Shen, M., Zhang, F., & Xie, J. (2017). Recent advances in momordica charantia: Functional components and biological activities. *International Journal of Molecular Sciences*, *18*(12). https://doi.org/10.3390/ijms18122555

Jorsal, T., Rungby, J., Knop, F. K., & Vilsboll, T. (2016). GLP-1 and Amylin in the Treatment of Obesity. *Current Diabetes Reports*, *16*(1), 1–7. https://doi.org/10.1007/s11892-015-0693-3

Joseph, B., & Jini, D. (2013). Antidiabetic effects of Momordica charantia (bitter melon) and its medicinal potency. *Asian Pacific Journal of Tropical Disease*, *3*(2), 93–102. https://doi.org/10.1016/S2222-1808(13)60052-3

Judprasong, K., Tanjor, S., Puwastien, P., & Sungpuag, P. (2011). Investigation of Thai plants for potential sources of inulin-type fructans. *Journal of Food Composition and Analysis*, *24*(4–5), 642–649. https://doi.org/10.1016/j.jfca.2010.12.001

Kalra, S. (2014). Sodium Glucose Co-Transporter-2 (SGLT2) Inhibitors: A Review of Their Basic and Clinical Pharmacology. *Diabetes Therapy*, *5*(2),

355–366. https://doi.org/10.1007/s13300-014-0089-4

Kalra, Sanjay. (n.d.). *Kalra*. 474–476.

Katirci, N., Işık, N., Güpür, Ç., Guler, H. O., Gursoy, O., & Yilmaz, Y. (2018). Differences in antioxidant activity, total phenolic and flavonoid contents of commercial and homemade tomato pastes. *Journal of the Saudi Society of Agricultural Sciences*, *xxxx*, 0–5. https://doi.org/10.1016/j.jssas.2018.11.003

Kato, C. G., De Almeida Gonçalves, G., Peralta, R. A., Seixas, F. A. V., De Sá-Nakanishi, A. B., Bracht, L., Comar, J. F., Bracht, A., & Peralta, R. M. (2017). Inhibition of α -Amylases by Condensed and Hydrolysable Tannins: Focus on Kinetics and Hypoglycemic Actions. *Enzyme Research*, *2017*. https://doi.org/10.1155/2017/5724902

Katsuma, S., Hirasawa, A., & Tsujimoto, G. (2005). Bile acids promote glucagon-like peptide-1 secretion through TGR5 in a murine enteroendocrine cell line STC-1. *Biochemical and Biophysical Research Communications*, *329*(1), 386–390. https://doi.org/10.1016/j.bbrc.2005.01.139

Khanna, P., Jain, S. C., Panagariya, A., & Dixit, V. P. (1981). Hypoglycemic activity of polypeptide-p from a plant source. *Journal of Natural Products*, *44*(6), 648–655. https://doi.org/10.1021/np50018a002

Kim, Y. A., Keogh, J. B., & Clifton, P. M. (2016). Polyphenols and glycémie control. *Nutrients*, *8*(1). https://doi.org/10.3390/nu8010017

Kirchhof, M., Popat, N., & Malowany, J. (2009). Diagnostic Review A Historical Perspective of the Diagnosis of Diabetes. *Universiti of Western Ontario Medical Journal*, *78*(1), 7–11.

Koupy, D., Kotolova, H., & Ruda-Kucerova, J. (2015). Effectiveness of phytotherapy in supportive treatment of type 2 diabetes mellitus II. Fenugreek (Trigonella foenum-graecum). *Ceska a Slovenska Farmacie*, *64*(September), 67–71.

Krentz, A. J., & Bailey, C. J. (2005). Oral antidiabetic agents: Current role in type 2 diabetes mellitus. *Drugs*, *65*(3), 385–411. https://doi.org/10.2165/00003495-200565030-00005

Krynski, I. A., & Logan, J. E. (1967). Dextrostix as a quantitative test for glucose in whole blood. *Canadian Medical Association Journal*, *97*(17), 1006–1011.

Kumar, N., Kaushik, N. K., Park, G., Choi, E. H., & Uhm, H. S. (2013). Enhancement of glucose uptake in skeletal muscle L6 cells and insulin secretion in pancreatic hamster-insulinoma-transfected cells by application of non-thermal plasma jet. *Applied Physics Letters*, *103*(20). https://doi.org/10.1063/1.4828742

Kumar, P., Kumar, S., & Janardan, S. (2013). Diabetes - A historical review. *Journal of Drug Delivery and Therapeutics*, *3*(1), 83–84.

Kumar, R., Balaji, S., Uma, T. S., & Sehgal, P. K. (2009). Fruit extracts of Momordica charantia potentiate glucose uptake and up-regulate Glut-4, PPARγ and PI3K. *Journal of Ethnopharmacology*, *126*(3), 533–537. https://doi.org/10.1016/j.jep.2009.08.048

Lakhtakia, R. (2013). The History of Diabetes Mellitus. *Textbook of Diabetes: Fourth Edition*, *13*(3), 368–370. https://doi.org/10.1002/9781444324808.ch1

Lankatillake, C., Huynh, T., & Dias, D. A. (2019). Understanding glycaemic control and current approaches for screening antidiabetic natural products from evidence-based medicinal plants. *Plant Methods*, *15*(1), 1–35. https://doi.org/10.1186/s13007-019-0487-8

Laranjeira, C., Nogueira, A., Almeida, R., Oliveira, A. ., Oliveira, R. ., Pinho, C., & Cruz, A. (2017). Antioxidant Activity and Cytotoxicity of Taraxacum Hispanicum Aqueous and Ethanolic Extracts on Hepg2 Cells. *International Journal of Pharmacognosy and Phytochemical Research*, *9*(1). https://doi.org/10.25258/ijpapr.v9i1.8031

Lebovitz, H. E. (2011). Insulin: Potential negative consequences of early routine use in patients with type 2 diabetes. *Diabetes Care*, *34*(SUPPL. 2). https://doi.org/10.2337/dc11-s225

Lee, J. O., Lee, S. K., Kim, J. H., Kim, N., You, G. Y., Moon, J. W., Kim, S. J., Park, S. H., & Kim, H. S. (2012). Metformin regulates glucose transporter 4 (GLUT4) translocation through AMP-activated protein kinase (AMPK)-mediated Cbl/CAP signaling in 3T3-L1 preadipocyte cells. *Journal of Biological Chemistry*, *287*(53), 44121–44129. https://doi.org/10.1074/jbc.M112.361386

Li, D., Zhang, Y., Liu, Y., Sun, R., & Xia, M. (2015). Purified Anthocyanin Supplementation Reduces Dyslipidemia, Enhances Antioxidant Capacity, and Prevents Insulin Resistance in Diabetic Patients. *The Journal of Nutrition*, *145*(4), 742–748. https://doi.org/10.3945/jn.114.205674

Linder, B., & Imperatore, G. (2013). Research updates on type 2 diabetes children. *NASN School Nurse (Print)*, *28*(3), 138–140. https://doi.org/10.1177/1942602X13479402

Ling, C., & Ronn, T. (2019). Epigenetics in Human Obesity and Type 2 Diabetes. *Cell Metabolism*, *29*(5), 1028–1044. https://doi.org/10.1016/j.cmet.2019.03.009

Loubatieres-Mariani, M. (2007). The discovery of hypoglycemic sulfonamides. *Journal of the Biological Society*, *201*(2), 121–125. https://doi.org/10.1051/jbio:2007014

Lourenço, S. C., Moldão-Martins, M., & Alves, V. D. (2019). Antioxidants of natural plant origins: From sources to food industry applications. *Molecules*, *24*(22), 14–16. https://doi.org/10.3390/molecules24224132

Luna, B., & Feinglos, M. N. (2001). Oral agents in the management of type 2 diabetes mellitus. *American Family Physician*, *63*(9), 1747–1756.

Luo, L., & Liu, M. (2016). Adipose tissue in control of metabolism. *Journal of Endocrinology*, *231*(3), R77–R99. https://doi.org/10.1530/JOE-16-0211

Marin-Penalver, J. J., Martin-Timon, I., Sevillano-Collantes, C., & Canizo-Gomez, F. J. del. (2016). Update on the treatment of type 2 diabetes mellitus. *World Journal of Diabetes*, *7*(17), 354. https://doi.org/10.4239/wjd.v7.i17.354

Maruyama, T., Tanaka, K., Suzuki, J., Miyoshi, H., Harada, N., Nakamura, T., Miyamoto, Y., Kanatani, A., & Tamai, Y. (2006). Targeted disruption of G protein-coupled bile acid receptor 1 (Gpbar1/M-Bar) in mice. *Journal of Endocrinology*, *191*(1), 197–205. https://doi.org/10.1677/joe.1.06546

Masiello, P., Broca, C., Gross, R., Roye, M., Manteghetti, M., Hillaire-Buys, D., Novelli, M., & Ribes, G. (1998). Experimental NIDDM: Development of a new model in adult rats administered streptozotocin and nicotinamide. *Diabetes*, *47*(2), 224–229. https://doi.org/10.2337/diab.47.2.224

Mason, S. A., Della Gatta, P. A., Snow, R. J., Russell, A. P., & Wadley, G. D. (2016). Ascorbic acid supplementation improves skeletal muscle oxidative stress and insulin sensitivity in people with type 2 diabetes: Findings of a randomized controlled study. *Free Radical Biology and Medicine*, *93*, 227–238. https://doi.org/10.1016/j.freeradbiomed.2016.01.006

Maulana, T. I., Falah, S., & Andrianto, D. (2019). Total phenolic content, total flavonoid content, and antioxidant activity of water and ethanol extract from Surian (Toona sinensis) leaves. *IOP Conference Series: Earth and Environmental Science*, *299*(1). https://doi.org/10.1088/1755-1315/299/1/012021

Meng, S., Cao, J., Feng, Q., Peng, J., & Hu, Y. (2013). Roles of chlorogenic Acid on regulating glucose and lipids metabolism: a review. *Evidence-Based Complementary and Alternative Medicine*, *2013*, 1–11.

Mishra, A., Gautam, S., Pal, S., Mishra, A., Rawat, A. K., Maurya, R., & Srivastava, A. K. (2015). Effect of Momordica charantia fruits on streptozotocin-induced diabetes mellitus and its associated complications. *International Journal of Pharmacy and Pharmaceutical Sciences*, *7*(3), 356–363.

Modak, M., Dixit, P., Londhe, J., Ghaskadbi, S., & Devasagayam, T. P. A. (2007). Indian herbs and herbal drugs used for the treatment of diabetes. *Journal of Clinical Biochemistry and Nutrition*, *40*(3), 163–173. https://doi.org/10.3164/jcbn.40.163

Modaresi, M., & Resalatpour, N. (2012). The effect of taraxacum officinale hydroalcoholic extract on blood cells in mice. *Advances in Hematology*, *2012*. https://doi.org/10.1155/2012/653412

Moen, M. F., Zhan, M., Hsu, V. D., Walker, L. D., Einhorn, L. M., Seliger, S. L., & Fink, J. C. (2009). Frequency of hypoglycemia and its significance in chronic kidney disease. *Clinical Journal of the American Society of Nephrology*, *4*(6), 1121–1127. https://doi.org/10.2215/CJN.00800209

Mohammed, R. A., Hassawi, D. S., & Ibaheem, N. K. (2018). Cytotoxic Activity of Taraxacum officinale Ethanolic Plant Extract against Human Breast Cancer (MCF-7) Cells and Human Hepatic (WRL-68) Cells. *Iraqi Journal of Cancer and Medicinal Genetics*, *11*(1), 16–21.

Monami, M., Nardini, C., & Mannucci, E. (2014). Efficacy and safety of sodium glucose co-transport-2 inhibitors in type 2 diabetes: A meta-analysis of randomized clinical trials. *Diabetes, Obesity and Metabolism*, *16*(5), 457–466. https://doi.org/10.1111/dom.12244

Montonen, J., Knekt, P., Järvinen, R., & Reunanen, A. (2004). Dietary Antioxidant Intake and Risk of Type 2 Diabetes. *Diabetes Care*, *27*(2), 362–366. https://doi.org/10.2337/diacare.27.2.362

Mumtaz, M. (2000). Gestational Diabetes Mellitus. *Malaysian Journal of Medicinal Sciences*, *7*(1), 4–9. https://doi.org/10.1353/vp.2005.0017

Murugesu, S., Ibrahim, Z., Ahmed, Q. U., Yusoff, N. I. N., Uzir, B. F., Perumal, V., Abas, F., Saari, K., El-Seedi, H., & Khatib, A. (2018). Characterization of ?-glucosidase inhibitors from clinacanthus nutans lindau leaves by gas chromatography-mass spectrometry-based metabolomics and molecular docking simulation. *Molecules*, *23*(9). https://doi.org/10.3390/molecules23092402

Mustapha, F. I., Azmi, S., Manaf, M. R. A., Hussein, Z., Mahir, N. J. N., Ismail, F., Aizuddin, A. N., & Goh, A. (2017). What are the direct medical costs of managing type 2 diabetes mellitus in Malaysia? *Medical Journal of Malaysia*, *72*(5), 271–277.

Nain, P., Saini, V., Sharma, S., & 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*(1), 65–71. https://doi.org/10.1016/j.jep.2012.04.014

Nathan, D. M., Buse, J. B., Davidson, M. B., Heine, R. J., Holman, R. R., Sherwin, R., & Zinman, B. (2006). Management of hyperglycemia in type 2 diabetes: A consensus algorithm for the initiation and adjustment of therapy. A consensus statement from the American diabetes association and the European association for the study of diabetes. *Diabetes Care*, *29*(8), 1963–1972. https://doi.org/10.2337/dc06-9912

National Health and Morbidity Survey. (2018). *National Health and Morbidity Survey (NHMS) 2018: Elderly Health. Vol. II: Elderly Health Findings: Vol. II*.

National Institute of Diabetes and Digestive and Kidney Diseases. (2018). *Sulfonylureas , First Generation*.

Nesto, R. ., Bell, D., Bonow, R. ., Fonseca, V., Grundy, S. ., Horton, E. ., Winter, M. ., Porte, D., Semenkovich, C. ., Smith, S., Young, L. ., & Kahn, R. (2004). Thiazolidinedione Use, Fluid Retention, and Congestive Heart Failure. A consensus statement from the American Heart Association and American Diabetes Association. *Diabetes Care and Circulation*, *27*(1), 256–263.

Onal, S., Timur, S., Okutucu, B., & Zihnioglu, F. (2005). Inhibition of α-glucosidase by aqueous extracts of some potent antidiabetic medicinal herbs. *Preparative Biochemistry and Biotechnology*, *35*(1), 29–36. https://doi.org/10.1081/PB-200041438

Ota, A., & Ulrih, N. P. (2017). An overview of herbal products and secondary metabolites used for management of type two diabetes. *Frontiers in Pharmacology*, *8*(JUL), 1–14. https://doi.org/10.3389/fphar.2017.00436

Otto-Buczkowska, E., Jarosz-Chobot, P., & Machnica, Ł. (2009). The role of amylin in glucose homeostasis regulation and possible future usage in adolescents with type 1 diabetes. *Diabetologia Doswiadczalna i Kliniczna*, *9*(2), 41–45.

Ouedraogo, M., Baudoux, T., Stevigny, C., Nortier, J., Colet, J. M., Efferth, T., Qu, F., Zhou, J., Chan, K., Shaw, D., Pelkonen, O., & Duez, P. (2012). Moustapha Ouedraogo_Toxicology tests.pdf. *Journal of Ethnopharmacology*, *140*, 492–512.

Panda, A., Jena, S., Sahu, P. K., Nayak, S., & Padhi, P. (2013). Effect of Polyherbal Mixtures on the Treatment of Diabetes. *ISRN Endocrinology*, *2013*, 1–5. https://doi.org/10.1155/2013/934797

Parasuraman, S., Thing, G. S., & Dhanaraj, S. A. (2014). Polyherbal formulation: Concept of ayurveda. *Pharmacognosy Reviews*, *8*(16), 73–80. https://doi.org/10.4103/0973-7847.134229

Patil, P., Mandal, S., Tomar, S. K., & Anand, S. (2015). Food protein-derived bioactive peptides in management of type 2 diabetes. *European Journal of Nutrition*, *54*(6), 863–880. https://doi.org/10.1007/s00394-015-0974-2

Petchi, R., Vijaya, C., & Parasuraman, S. (2014). Antidiabetic activity of polyherbal formulation in streptozotocin- Nicotinamide induced diabetic wistar rats. *Journal of Traditional and Complementary Medicine*, *4*(2), 108–117. https://doi.org/10.4103/2225-4110.126174

Petersen, M. (2003). Economic costs of diabetes in the U.S. in 2002. In *Diabetes Care* (Vol. 26, Issue 3, pp. 917–932). https://doi.org/10.2337/diacare.26.3.917

Pham, T., Ngo, D., Ngo, D., & Vo, T. (2019). *Investigation of Biological Activities of Wild Bitter*. 1–10.

Pitchakarn, P., Ogawa, K., Suzuki, S., Takahashi, S., Asamoto, M., Chewonarin, T., Limtrakul, P., & Shirai, T. (2010). Momordica charantia leaf extract suppresses rat prostate cancer progression in vitro and in vivo. *Cancer Science*, *101*(10), 2234–2240. https://doi.org/10.1111/j.1349-7006.2010.01669.x

Pitipanapong, J., Chitprasert, S., Goto, M., Jiratchariyakul, W., Sasaki, M., & Shotipruk, A. (2007). New approach for extraction of charantin from Momordica charantia with pressurized liquid extraction. *Separation and Purification Technology*, *52*(3), 416–422. https://doi.org/10.1016/j.seppur.2005.11.037

Rajendiran, D., Packirisamy, S., & Gunasekaran, K. (2018). A review on role of antioxidants in diabetes. *Asian Journal of Pharmaceutical and Clinical Research*, *11*(2), 48–53. https://doi.org/10.22159/ajpcr.2018.v11i2.23241

Rashmi, S., & Shilpy, S. (2016). Herbs and Botanical Ingredients with Beneficial Effects on Blood Sugar Levels in Pre-diabetes. *Herbal Medicine: Open Access*, *2*(1). https://doi.org/10.21767/2472-0151.100011

Rena, G., Hardie, D. G., & Pearson, E. R. (2017). The mechanisms of action of metformin. *Diabetologia*, *60*(9), 1577–1585. https://doi.org/10.1007/s00125-017-4342-z

Richmond, R. A., Vuong, Q. V., & Scarlett, C. J. (2017). Cytotoxic Effect of Bitter Melon (Momordica charantia L.) Ethanol Extract and Its Fractions on Pancreatic Cancer Cells in vitro. *Exploratory Research and Hypothesis in Medicine*, *2*(4), 1–11. https://doi.org/10.14218/erhm.2017.00032

Rizvi, S. I., & Mishra, N. (2013). Traditional Indian medicines used for the management of diabetes mellitus. *Journal of Diabetes Research*, *2013*. https://doi.org/10.1155/2013/712092

Roffey, B. W. C., Atwal, A. S., Johns, T., & Kubow, S. (2007). Water extracts from Momordica charantia increase glucose uptake and adiponectin secretion in 3T3-L1 adipose cells. *Journal of Ethnopharmacology*, *112*, 77–84. https://doi.org/10.1016/j.jep.2007.02.003

Sabina, E., Zaidul, I. S. M., Ghafoor, K., Jaffri, J. M., Sahena, F., Babiker, E. E., Perumal, V., Hamed, M., Amid, M., & Khatib, A. (2016). Screening of Various Parts of Phaleria macrocarpa Plant for α-Glucosidase Inhibitory Activity. *Journal of Food Biochemistry*, *40*(2), 201–210. https://doi.org/10.1111/jfbc.12212

Sacks, D. B. (2011). A1C versus glucose testing: A comparison. *Diabetes Care*, *34*(2), 518–523. https://doi.org/10.2337/dc10-1546

Saeed, F., Afzaal, M., Niaz, B., Arshad, M. U., Tufail, T., Hussain, M. B., & Javed, A. (2018). Bitter melon (Momordica charantia): A natural healthy vegetable. *International Journal of Food Properties*, *21*(1), 1270–1290. https://doi.org/10.1080/10942912.2018.1446023

Saeed, N., Khan, M. R., & Shabbir, M. (2012). Antioxidant activity, total phenolic and total flavonoid contents of whole plant extracts Torilis leptophylla L. *BMC Complementary and Alternative Medicine*, *12*(1), 1174. https://doi.org/10.1186/1472-6882-12-221

Salehi, B., Ata, A., Kumar, N. V. A., Sharopov, F., Ramírez-Alarcón, K., Ruiz-Ortega, A., Ayatollahi, S. A., Fokou, P. V. T., Kobarfard, F., Zakaria, Z. A., Iriti, M., Taheri, Y., Martorell, M., Sureda, A., Setzer, W. N., Durazzo, A., Lucarini, M., Santini, A., Capasso, R., … Sharifi-Rad, J. (2019). Antidiabetic potential of medicinal plants and their active components. In *Biomolecules* (Vol. 9, Issue 10). MDPI AG. https://doi.org/10.3390/biom9100551

Santos, A. K. L., Costa, J. G. M., Menezes, I. R. A., Cansanção, I. F., Santos, K. K. A., Matias, E. F. F., & Coutinho, H. D. M. (2010). Antioxidant activity of five Brazilian plants used as traditional medicines and food in Brazil. *Pharmacognosy Magazine*, *6*(24), 335–338. https://doi.org/10.4103/0973-1296.71789

Saudek, C. D., Herman, W. H., Sacks, D. B., Bergenstal, R. M., Edelman, D., & Davidson, M. B. (2008). A new look at screening and diagnosing diabetes mellitus. *Journal of Clinical Endocrinology and Metabolism*, *93*(7), 2447–2453. https://doi.org/10.1210/jc.2007-2174

Saxena, A. K., Srivastava, P., Kale, R. K., & Baquer, N. Z. (1993). Impaired antioxidant status in diabetic rat liver. Effect of vanadate. *Biochemical Pharmacology*, *45*(3), 539–542. https://doi.org/10.1016/0006-2952(93)90124-F

Scheen, A. J. (2015). Pharmacodynamics, efficacy and safety of sodium-glucose co-transporter type 2 (SGLT2) inhibitors for the treatment of type 2 diabetes mellitus. *Drugs*, *75*(1), 33–59. https://doi.org/10.1007/s40265-014-0337-y

Schumacher, S., Abbasi, I., Weise, D., Hatorp, V., Sattler, K., Sieber, J., & Hasslacher, C. (2001). Single- and multiple-dose pharmacokinetics of repaglinide in patients with type 2 diabetes and renal impairment. *European Journal of Clinical Pharmacology*, *57*(2), 147–152. https://doi.org/10.1007/s002280100280

Schutz, K., Carle, R., & Schieber, A. (2006). Taraxacum-A review on its phytochemical and pharmacological profile. *Journal of Ethnopharmacology*, *107*(3), 313–323. https://doi.org/10.1016/j.jep.2006.07.021

Schutz, K., Muks, E., Carle, R., & Schieber, A. (2006). Separation and quantification of inulin in selected artichoke (Cynara scolymus L.) cultivars and dandelion (Taraxacum officinale WEB. ex WIGG.) roots by high-performance anion exchange chromatography with pulsed amperometric detection. *Biomedical Chromatography*, *20*(3), 1295–1303. https://doi.org/10.1002/bmc

Sekhon-Loodu, S., & Rupasinghe, H. P. V. (2019). Evaluation of antioxidant,

antidiabetic and antiobesity potential of selected traditional medicinal plants. *Frontiers in Nutrition*, *6*(April), 1–11. https://doi.org/10.3389/fnut.2019.00053

Sharifi-Rad, M., Roberts, T. H., Matthews, K. R., Bezerra, C. F., Morais-Braga, M. F. B., Coutinho, H. D. M., Sharopov, F., Salehi, B., Yousaf, Z., Sharifi-Rad, M., del Mar Contreras, M., Varoni, E. ., Verma, D. R., Iriti, M., & Sharifi-Rad, J. (2018). Ethnobotany of the genus Taraxacum—Phytochemicals and antimicrobial activity. *Phytotherapy Research*, *32*(11), 2131–2145. https://doi.org/10.1002/ptr.6157

Sharma, K., & Zafar, R. (2014). Simultaneous estimation of Taraxerol and Taraxasterol in root callus cultures of Taraxacum officinale Weber. *International Journal of Pharmacognosy and Phytochemical Research*, *6*(3), 540–546.

Sheng, S. B., Shah, W. M., & Hassan, N. B. A. (2019). Chapter 1: What is diabetes? In *IDF Diabetes Atlas - 8th Edition* (Vol. 1908, Issue January, pp. 2–6).

Sherwani, S. I., Khan, H. A., Ekhzaimy, A., Masood, A., & Sakharkar, M. K. (2016). Significance of HbA1c test in diagnosis and prognosis of diabetic patients. *Biomarker Insights*, *11*, 95–104. https://doi.org/10.4137/Bmi.s38440

Shih, C. C., Lin, C. H., Lin, W. L., & Wu, J. Bin. (2009). Momordica charantia extract on insulin resistance and the skeletal muscle GLUT4 protein in fructose-fed rats. *Journal of Ethnopharmacology*, *123*(1), 82–90. https://doi.org/10.1016/j.jep.2009.02.039

Singh, A. K., Jatwa, R., & Joshi, J. (2014). Cytoprotective and dipeptidyl peptidase IV (DPP-IV/CD26) inhibitory roles of Ocimum sanctum and Momordica charantia extract. *Asian Journal of Pharmaceutical and Clinical Research*, *7*(SUPPL. 1), 115–120.

Singh, J., Cumming, E., Manoharan, G., Kalasz, H., & Adeghate, E. (2011). Medicinal Chemistry of the Anti-Diabetic Effects of Momordica Charantia: Active Constituents and Modes of Actions. *The Open Medicinal Chemistry Journal*, *5*(Suppl 2), 70–77. https://doi.org/10.2174/1874104501105010070

Smith, J. J., Shah, S. A., & Cochran, D. S. (2018). Prevention, Early Detection, and Reversal of Type-2 Diabetes using Collective System Design. *MATEC Web of Conferences*, *223*, 1–10. https://doi.org/10.1051/matecconf/201822301018

Sola, D., Rossi, L., Schianca, G. P. C., Maffioli, P., Bigliocca, M., Mella, R., Corlianò, F., Paolo Fra, G., Bartoli, E., & Derosa, G. (2015). Sulfonylureas and their use in clinical practice. *Archives of Medical Science*, *11*(4), 840–848. https://doi.org/10.5114/aoms.2015.53304

Sornalakshmi, V., Tresina Soris, P., Paulpriya, K., Packia Lincy, M., & Mohan, V. R. (2016). Oral glucose tolerance test (OGTT) in normal control and glucose induced hyperglycemic rats with hedyotis leschenaultiana DC. *International Journal of Toxicological and Pharmacological Research*, *8*(1), 59–62.

Srivastava, S., Lal, V. K., & Pant, K. K. (2012). *Polyherbal formulations based on Indian medicinal plants as antidiabetic phytotherapeutics*. *2*(1), 1–15.

Sun, F., Chai, S., Yu, K., Quan, X., Yang, Z., Wu, S., Zhang, Y., Ji, L., Wang, J. U., & Shi, L. (2015). Gastrointestinal adverse events of glucagon-like peptide-1 receptor agonists in patients with type 2 diabetes: A systematic review and network meta-analysis. *Diabetes Technology and Therapeutics*, *17*(1), 35–42. https://doi.org/10.1089/dia.2014.0188

Tahira, S., & Hussain, F. (2014). Antidiabetic evaluation of Momordica charantia L fruit extracts. *West Indian Medical Journal*, *63*(4), 294–299. https://doi.org/10.7727/wimj.2013.180

Tailor, C. S., & Goyal, A. (2014). Antioxidant Activity by DPPH Radical Scavenging Method of Ageratum conyzoides Linn. Leaves. *American Journal of Ethnomedicine*, *1*(4), 244–249. https://doi.org/10.1016/S0029-5493(01)00385-5

Tan, C. Y., & Vidal-Puig, A. (2008). Adipose tissue expandability: The metabolic problems of obesity may arise from the inability to become more obese. *Biochemical Society Transactions*, *36*(5), 935–940. https://doi.org/10.1042/BST0360935

Tan, D. C., Idris, K. I., Kassim, N. K., Lim, P. C., Safinar Ismail, I., Hamid, M., & Ng, R. C. (2019). Comparative study of the antidiabetic potential of Paederia foetida twig extracts and compounds from two different locations in Malaysia. *Pharmaceutical Biology*, *57*(1), 345–354. https://doi.org/10.1080/13880209.2019.1610462

Tan, E. S., Abdullah, A., & Maskat, M. Y. (2013). Effect of drying methods on total antioxidant capacity of bitter gourd (Momordica charantia) fruit. *AIP Conference Proceedings*, *1571*(November), 710–716. https://doi.org/10.1063/1.4858738

Tan, K. L. (2019). Factors influencing physical inactivity among adults in negeri sembilan, peninsular malaysia. *Medical Journal of Malaysia*, *74*(5), 389–393.

Tan, M. Y., & Magarey, J. (2008). Self-care practices of Malaysian adults with diabetes and sub-optimal glycaemic control. *Patient Education and Counseling*, *72*(2), 252–267. https://doi.org/10.1016/j.pec.2008.03.017

Tan, P. W., Tan, C. P., & Ho, C. W. (2011). Antioxidant properties: Effects of solid-to-solvent ratio on antioxidant compounds and capacities of pegaga (Centella asiatica). *International Food Research Journal*, *18*(2), 557–562.

Tan, S. P., Parks, S. E., Stathopoulos, C. E., & Roach, P. D. (2014). Extraction of Flavonoids from Bitter Melon. *Food and Nutrition Sciences*, *05*(05), 458–465. https://doi.org/10.4236/fns.2014.55054

Tessier, D., Dawson, K., Tétrault, J. P., Bravo, G., & Meneilly, G. S. (1994). Glibenclamide vs Gliclazide in Type 2 Diabetes of the Elderly. *Diabetic Medicine*, *11*(10), 974–980. https://doi.org/10.1111/j.1464-5491.1994.tb00256.x

Thomas, C., Pellicciari, R., Pruzanski, M., Auwerx, J., & Schoonjans, K. (2008). Targeting bile-acid signalling for metabolic diseases. *Nature Reviews Drug Discovery*, *7*(8), 678–693. https://doi.org/10.1038/nrd2619

Thornberry, N. A., & Gallwitz, B. (2009). Mechanism of action of inhibitors of dipeptidyl-peptidase-4 (DPP-4). *Best Practice and Research: Clinical Endocrinology and Metabolism*, *23*(4), 479–486. https://doi.org/10.1016/j.beem.2009.03.004

Tonyushkina, K., & Nichols, J. H. (2009). Glucose meters: A review of technical challenges to obtaining accurate results. *Journal of Diabetes Science and Technology*, *3*(4), 971–980. https://doi.org/10.1177/193229680900300446

Toplak, H., Hoppichler, F., Wascher, T. C., Schindler, K., & Ludvik, B. (2016). Obesity and type 2 diabetes. In *Wiener Klinische Wochenschrift* (Vol. 128). https://doi.org/10.1007/s00508-016-0986-9

Tousch, D., Lajoix, A. D., Hosy, E., Azay-Milhau, J., Ferrare, K., Jahannault, C., Cros, G., & Petit, P. (2008). Chicoric acid, a new compound able to enhance insulin release and glucose uptake. *Biochemical and Biophysical Research Communications*, *377*(1), 131–135. https://doi.org/10.1016/j.bbrc.2008.09.088

Truong, D.-H., Nguyen, H., Thuy, N., Ta, A., Bui, A. V., Do, H., & Nguyen, H. C. (2019). *Evaluation of the Use of Different Solvents for Phytochemical Constituents, Antioxidants, and In Vitro Anti-Inflammatory Activities of Severinia buxifolia*. https://doi.org/10.1155/2019/8178294

Tuomilehto, J., Lindstrom, J., Eriksson, J. ., Valle, T. ., Hamalainen, H., Ilanne-Parikka, P., Keinanen-Kiukaanniemi, S., Laakso, M., Louheranta, A., Rastas, M., Salminen, V., & Uusitupa, M. (2001). Prevention of Type 2 Diabetes Mellitus By Changes in Lifestyle Among Subjects With Impaired Glucose Tolerance. *The New England Jounal of Medi*, *344*(18), 1343–1350.

Ukom, A. N., Ojimelukwe, P. C., Ezeama, C. F., Ortiz, D. O., & Aragon, I. . (2014). Phenolic content and antioxidant activity of some under-utilized Nigerian yam (Dioscorea spp.) and cocoyam (Xanthosomamaffa (scoth)) tubers. *IOSR Journal of Environmental Science, Toxicology and Food Technology*, *8*(7), 104–111. https://doi.org/10.9790/2402-0871104111

Valla, V. (2010). Therapeutics of diabetes mellitus: focus on insulin analogues

and insulin pumps. *Experimental Diabetes Research*, *2010*, 178372. https://doi.org/10.1155/2010/178372

van de Laar, F. ., Lucassen, P. ., Akkermans, R. ., van de Lisdonk, E. ., Rutten, G. ., & van Weel, C. (2005). Reviews / Commentaries / ADA Statements ␣ -Glucosidase Inhibitors for Patients Results from a Cochrane systematic review and meta-analysis. *Diabetes Care*, *28*(1), 154–163.

Vella, A. (2012). Mechanism of action of DPP-4 inhibitors - New insights. *Journal of Clinical Endocrinology and Metabolism*, *97*(8), 2626–2628. https://doi.org/10.1210/jc.2012-2396

Vigneri, P., Frasca, F., Sciacca, L., Pandini, G., & Vigneri, R. (2009). Diabetes and cancer. *Endocrine-Related Cancer*, *16*(4), 1103–1123. https://doi.org/10.1677/ERC-09-0087

Virdi, J., Sivakami, S., Shahani, S., Suthar, A. C., Banavalikar, M. M., & Biyani, M. K. (2003). Antihyperglycemic effects of three extracts from Momordica charantia. *Journal of Ethnopharmacology*, *88*(1), 107–111. https://doi.org/10.1016/S0378-8741(03)00184-3

Walters, T. ., & Decker-Walter, D. . (1988). Balsam-Pear (Momordica charantia, Cucurbitaceae). *Economic Botany*, *42*(2), 286–288.

Wang, H. J., Xiang, Y., Phd, J., Shen, W., Neng, J., Wu, T., Li, Y. J., & Fu, W. (2007). Low dose streptozotocin (STZ) combined with high energy intake can effectively induce type 2 diabetes through altering the related gene expression. In *Asia Pac J Clin Nutr* (Vol. 16, Issue 1).

Wang, Y. H., Avula, B., Liu, Y., & Khan, I. A. (2008). Determination and quantitation of five cucurbitane triterpenoids in Momordica charantia by reversed-phase high-performance liquid chromatography with evaporative light scattering detection. *Journal of Chromatographic Science*, *46*(2), 133–136. https://doi.org/10.1093/chromsci/46.2.133

Webb, D. ., Davies, M., & Khunti, K. (2018). Sulfonylureas: historic to contemporary role in the management of type 2 diabetes. *Medicographia*, *40*(4), 129–135.

White, P. A. S., Oliveira, R. C. M., Oliveira, A. P., Serafini, M. R., Araújo, A. A. S., Gelain, D. P., Moreira, J. C. F., Almeida, J. R. G. S., Quintans, J. S. S., Quintans-Junior, L. J., & Santos, M. R. V. (2014). Antioxidant activity and mechanisms of action of natural compounds isolated from lichens: A systematic review. *Molecules*, *19*(9), 14496–14527. https://doi.org/10.3390/molecules190914496

Whitmore, C. (2010). Type 2 diabetes and obesity in adults. *British Journal of Nursing*, *19*(14), 0. https://doi.org/10.7326/acpjc-2016-165-2-010

Wirngo, F. E., Lambert, M. N., & Jeppesen, P. B. (2016). The physiological effects of dandelion (Taraxacum officinale) in type 2 diabetes. *Review of*

Diabetic Studies, *13*(2–3), 113–131. https://doi.org/10.1900/RDS.2016.13.113

World Health Organization. (2006). Definition and Diagnosis of Diabetes Mellitus and Intermediate Hyperglycemia. In *World Health Organization*. https://doi.org/10.1016/0005-2736(75)90130-3

World Health Organization. (2016). Global Report on Diabetes. In *World Health Organization* (Vol. 978). https://sci-hub.si/https://apps.who.int/iris/handle/10665/204874%0Ahttps://apps.who.int/iris/bitstream/handle/10665/204874/WHO_NMH_NVI_16.3_eng.pdf?sequence=1%0Ahttp://www.who.int/about/licensing/copyright_form/index.html%0Ahttp://www.who.int/about/licens

Wu, S. J., & Ng, L. T. (2008). Antioxidant and free radical scavenging activities of wild bitter melon (Momordica charantia Linn. var. abbreviata Ser.) in Taiwan. *LWT - Food Science and Technology*, *41*(2), 323–330. https://doi.org/10.1016/j.lwt.2007.03.003

Xu, D. P., Li, Y., Meng, X., Zhou, T., Zhou, Y., Zheng, J., Zhang, J. J., & Li, H. Bin. (2017). Natural antioxidants in foods and medicinal plants: Extraction, assessment and resources. *International Journal of Molecular Sciences*, *18*(1), 20–31. https://doi.org/10.3390/ijms18010096

Xu, X., Su, S., Barnes, V. A., De Miguel, C., Pollock, J., Ownby, D., Shi, H., Zhu, H., Snieder, H., & Wang, X. (2013). A genome-wide methylation study on obesity: Differential variability and differential methylation. *Epigenetics*, *8*(5), 522–533. https://doi.org/10.4161/epi.24506

Yamaoka-Tojo, M., Tojo, T., & Izumi, T. (2008). Beyond Cholesterol Lowering: Pleiotropic Effects of Bile Acid Binding Resins Against Cardiovascular Disease Risk Factors in Patients with Metabolic Syndrome. *Current Vascular Pharmacology*, *6*(4), 271–281. https://doi.org/10.2174/157016108785909698

Yammine, L., Kosten, T. R., Pimenova, M., & Schmitz, J. M. (2019). Cigarette smoking, type 2 diabetes mellitus, and glucagon-like peptide-1 receptor agonists as a potential treatment for smokers with diabetes: An integrative review. *Diabetes Research and Clinical Practice*, *149*, 78–88. https://doi.org/10.1016/j.diabres.2019.01.033

Yap, A., Nishiumi, S., Yoshida, K.-I., & Ashida, H. (2007). Rat L6 myotubes as an in vitro model system to study GLUT4-dependent glucose uptake stimulated by inositol derivatives. *Cytotechnology*, *55*(2–3), 103–108. https://doi.org/10.1007/s10616-007-9107-y

Yarnell, E., & Abascal, K. (1999). Taraxacum officinale. *Alternative Medicine Review*, *4*(2), 112–114. https://doi.org/10.1055/s-2006-934717

Yarnell, E., & Abascal, K. (2009). Dandelion (Taraxacum officinale and T mongolicum). *Integrative Medicine: A Clinician's Journal*, *8*(2), 35–38.

http://web.ebscohost.com.ezproxy.endeavour.edu.au:2048/ehost/pdfviewer/pdfviewer?sid=310d10e0-58b6-4003-9b7c-c9b473f21f34%40sessionmgr14&vid=6&hid=25

Yusri, N., Chan, K., Iqbal, S., & Ismail, M. (2012). Phenolic Content and Antioxidant Activity of Hibiscus cannabinus L. Seed Extracts after Sequential Solvent Extraction. *Molecules*, *17*(11), 12612–12621. https://doi.org/10.3390/molecules171112612

Zaini, A. (2000). Where is Malaysia in the midst of the Asian epidemic of diabetes mellitus? *Diabetes Research and Clinical Practice*, *50*(SUPPL. 2), 23–28. https://doi.org/10.1016/S0168-8227(00)00175-3

Zhang, M., Hettiarachchy, N. S., Horax, R., Chen, P., & Over, K. F. (2009). Effect of maturity stages and drying methods on the retention of selected nutrients and phytochemicals in bittermelon (momordica charantia) Leaf. *Journal of Food Science*, *74*(6), C441–C448. https://doi.org/10.1111/j.1750-3841.2009.01222.x

Zhang, P., Zhang, X., Brown, J., Vistisen, D., Sicree, R., Shaw, J., & Nichols, G. (2010). Global healthcare expenditure on diabetes for 2010 and 2030. *Diabetes Research and Clinical Practice*, *87*(3), 293–301. https://doi.org/10.1016/j.diabres.2010.01.026

Zhang, Q., Yu, H., Xiao, X., Hu, L., Xin, F., & Yu, X. (2018). Inulin-type fructan improves diabetic phenotype and gut microbiota profiles in rats. *PeerJ*, *2018*(3). https://doi.org/10.7717/peerj.4446

Zhang, S., Bi, H., & Liu, C. (2007). Extraction of bio-active components from Rhodiola sachalinensis under ultrahigh hydrostatic pressure. *Separation and Purification Technology*, *57*(2), 277–282. https://doi.org/10.1016/J.SEPPUR.2007.04.022

Zhao, G. T., Liu, J. Q., Deng, Y. Y., Li, H. Z., Chen, J. C., Zhang, Z. R., Zhou, L., & Qiu, M. H. (2014). Cucurbitane-type triterpenoids from the stems and leaves of Momordica charantia. *Fitoterapia*, *95*, 75–82. https://doi.org/10.1016/j.fitote.2014.03.005

Zhao, P., Ming, Q., Xiong, M., Song, G., Tan, L., Tian, D., Liu, J., Huang, Z., Ma, J., Shen, J., Liu, Q.-H., & Yang, X. (2018). Dandelion Chloroform Extract Promotes Glucose Uptake via the AMPK/GLUT4 Pathway in L6 Cells. *Evidence-Based Complementary and Alternative Medicine*, *2018*, 1–10. https://doi.org/10.1155/2018/1709587

Zou, C., Wang, Y., & Shen, Z. (2005). 2-NBDG as a fluorescent indicator for direct glucose uptake measurement. *Journal of Biochemical and Biophysical Methods*, *64*(3), 207–215. https://doi.org/10.1016/J.JBBM.2005.08.001

BIODATA OF STUDENT

Nithiyaa Perumal was born in Kuala Lumpur. She obtained her BSc (Hons) degree from Universiti Malaysia Terengganu in 2008. She then went on to pursue her Masters in Mycology and Plant Pathology from the Department of Biology, Faculty of Science, Universiti Putra Malaysia. Upon completion of her MSc degree, she worked as a Research Assistant with a private company for two years before continuing PhD in the field of Plant and Animal Physiology, specifically in the study of Diabetes in the same Department. Due to interest in teaching, she served as a part-time instructor for various undergraduate courses in the Department of Biology during her postgraduate years. She has also attended several self-empowering workshops such as Scientific Writing skills, Systematic Review and Meta-Analysis workshop, Data Analytics workshops as well as Seminar on Preparation for Viva. Throughout the PhD candidature, she has also attended conferences such as Fundamental Science Congress (FSE) and i-Simbiomas, organized under UPM.

LIST OF PUBLICATIONS

I. Publication in Scientific Journal

Perumal, N., Nallappan, M., Shohaimi, S., Kassim, N. K., Tee, T. T., & Cheah, Y. H. (2022). Synergistic Antidiabetic Activity of *Taraxacum officinale* (L.) Weber ex F.H.Wigg and *Momordica charantia* L. Polyherbal Combination. *Biomedicine & Pharmacotherapy*, 145, 112401.

II. Papers Presented at Seminar/ Conference

Perumal, N., Nallappan, M., Shohaimi, S., & Kassim, N. K. *Efficacy of Taraxacum officinale and Momordica charantia extracts in inhibiting dipeptidyl peptidase IV [DPP (IV)] enzyme*. Paper presented at the Fundamental Science Congress, Faculty of Veterinary Medicine, Universiti Putra Malaysia. November 2015.

Perumal, N., Nallappan, M., Shohaimi, S., Kassim, N. K., Tee, T. T., & Cheah, Y. H. *Dipeptidyl peptidase IV (DPP IV) inhibitory activity screening of Momordica charantia, Taraxacum officinale and Trigonella foenum-graecum extracts in vitro*. Paper presented at the Malaysia International Symposium on Biological, Putrajaya International Convention Centre (PICC), Putrajaya. October 2016.

Perumal, N., & Nallappan, M. *Synergistic in vitro Antidiabetic Efficacy of Dual Herbal Combination of Taraxacum officinale (L.) Weber ex F.H.Wigg and Momordica charantia L.* Paper presented at the Asian Symposium on Medicinal Plants and Spices XVII, Virtual Conference by Malaysian Natural Products Society. August 2021.