UNIVERSITI PUTRA MALAYSIA

ELUCIDATION ON ANTIOXIDANT AND ANTIDIABETIC ACTIVITIES OF Curculigo latifolia DRYAND VIA IN VITRO AND MOLECULAR DOCKING

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By

NUR ATHIRAH BINTI ZABIDI

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Type 2 diabetes mellitus (T2DM) is a heterogeneous metabolic disorder, causing various health complications, and apparently affects the human's life. The controversy over taking antidiabetic medications for diabetic patients has a definite side effect on either short-term or long-term effects. Despite a wide solution that has revealed in providing systematic relief in T2DM, considerable research attention has been focussing on exploring a better therapeutic alternative research that generally employed to increase antidiabetic values from the natural plant extract. The aim of the current study was to elucidate on antioxidant and antidiabetic activities on root and fruit extracts of *Curculigo latifolia* via *in vitro* and molecular docking studies. The evaluation in the phytochemical and antioxidant activity has been assessed by total flavonoid content (TFC), total phenolic content (TPC), 2, 2′-azino-bis-3-ethylbenzthiazoline-6-sulphonic acid (ABTS) and 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical. Besides, antidiabetic activity was subsequently explored based on the inhibition of α-amylase, α-glucosidase and dipeptidyl peptidase (IV) assay, along with *in vitro* studies through glucose uptake activity, insulin secretion assay and screening agonist of Peroxisome proliferator-activated receptor gamma (PPAR-γ). Then, the activity of the protein was further assessed through molecular docking analysis with the selected ligands from the screening of compounds using liquid chromatography-mass spectrometry (LCMS). The effect of subcritical water extraction (SWE) temperature on TPC, TFC and antioxidant capacity (ABTS & DPPH) shows a significant ($p < 0.05$) while the extraction's times shows no significant effect.The highest results for the root extracts recorded with extraction yield (36.5g/100g), TPC (92.55 mg GAE/g), TFC (13.26 mg RE/g) ABTS (66.8 mg trolox equiv/g) and DPPH (128.7 mg trolox equiv/g) at 180^{o}C and 30 minutes extraction time. Conversely, the highest results for the fruit extracts recorded with extraction yield (16.7g/100g), TPC (78.63 mg GAE/g), TFC (5.79 mg RE/g) ABTS (54.8 mg trolox equiv/g) and DPPH (127.3 mg trolox equiv/g) also at 180^{o}C and 90 minutes extraction time. Moreover, a significant positive correlation between TPC, TFC and antioxidant capacity (DPPH and ABTS) values was detected for both of the extracts. In an enzymatic assay, both extracts show a significant positive inhibition ($p < 0.05$). The highest inhibition by the roots extracts with α-glucosidase (IC_{50} 2.72±1.43 mg/ml), α-amylase (IC_{50} 0.31±2.31 mg/ml), DPP (IV) (IC_{50} 3.9±0.95 mg/ml) compared with fruit extract that recorded with α-glucosidase (IC_{50} 5.6±0.66 mg/ml), α-amylase (IC_{50} 1.3±0.75 mg/ml), DPP (IV) (IC_{50} 5.7±0.66 mg/ml). In addition, both of the extracts caused a significant increase ($p< 0.05$) in glucose uptake activity in adipocyte 3T3-L1 and L6 cell lines. The highest glucose uptake by 3T3-L1 for the root and fruits extract was 67% and 49% respectively. Meanwhile, the highest glucose uptake by L6 muscle cells for the root extract was 85% while for the fruit extract was 68%. Besides, both of the extracts displayed a significant increase ($p< 0.05$) in insulin secretion with the highest activity by the root and fruit was 13.74 µg/ml and 11.06 µg/ml respectively in pancreatic BRIN-BD11cell line. The results on the screening of ppar-γ agonist assay show that root extracts exhibit 25%, and fruit extracts give 14% significance with $p \leq 0.05$ by comparing both of the extracts. Molecular docking results indicated that phlorizin, scandenin, pomiferin and mundulone were selected as a potential inhibitor in most of the targeted protein by having the least binding energy and some of these ligands were observed that interact with crucial residues in the active site region of the protein. In conclusion, the present study indicated that there is potential in the development of *C. latifolia* as a therapeutic alternative agent for T2DM management, particularly by benefiting the simultaneous targeting in the main mechanism of action in T2DM.

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

KAJIAN AKTIVITI ANTIOKSIDAN DAN ANTIDIABETES *Curculigo latifolia* DRYAND MELALUI KAJIAN *IN VITRO* DAN *DOCKING* MOLEKUL

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Diabetes melitus jenis 2 (T2DM) adalah gangguan metabolik heterogen yang menyebabkan pelbagai komplikasi kesihatan dan turut memberi kesan kepada kehidupan manusia. Kontroversi dalam pengambilan ubat antidiabetik untuk pesakit diabetes mempunyai kesan sampingan sama ada untuk jangka pendek atau jangka panjang. Walaupun terdapat penyelesaian yang luas dalam memberi bantuan sistematik untuk T2DM, fokus penyelidikan masa kini tertumpu dalam penerokaan kajian alternatif terapeutik yang lebih baik dan kebiasaanya digunakan dengan meningkatkan nilai antioksidan dan antidiabetik daripada ekstrak tumbuhan semulajadi. Tujuan kajian semasa adalah untuk mengkaji aktiviti antioksidan dan antidiabetik pada ekstrak akar dan buah *Curculigo latifolia* melalui kajian *in vitro* dan penyelidikan *docking* molekul. Penilaian terhadap ujian fitokimia dan aktiviti antioksidan dianalisis menggunakan jumlah kandungan flavonoid (TFC), jumlah kandungan phenolic (TPC), radikal 2, 2′-azino-bis-3-etilbenzilthiazoline-6-sulphonic acid (ABTS) dan 1,1-difenil-2-pikrilhidrazil (DPPH). Selain itu, aktiviti antidiabetik kemudiannya diterokai berdasarkan perencatan enzim α-amilase, α-glukosidase dan asai dipeptidil peptidase (IV), bersama-sama dengan kajian *in vitro* melalui aktiviti pengambilan glukosa, ujian rembesan insulin dan pemeriksaan agonis *Peroxisome proliferator-aktivated reseptor gamma* (PPAR-γ). Kemudian, aktiviti protein yang terlibat dalam antidiabetes telah dikaji dengan lebih lanjut melalui analisis *docking* molekul dan ligan dipilih berdasarkan penyaringan sebatian dengan menggunakan kromatografi cecair- spektrometri jisim (LCMS). Kesan suhu pengekstrakan air subkritical (SWE) pada TPC, TFC dan kapasiti antioksidan (ABTS & DPPH) menunjukkan signifikan ($p <0.05$) sementara masa pengekstrakan tidak menunjukkan kesan yang signifikan. Hasil tertinggi untuk ekstrak akar dicatatkan dengan hasil pengekstrakan (36.5g / 100g), TPC (92.55 mg GAE / g), TFC (13.26 mg RE / g) ABTS (66.8 mg trolox equiv/g) dan DPPH (128.7 mg trolox equiv/g) pada suhu

pengekstrakan 180°C dan 30 minit. Sebaliknya, hasil tertinggi untuk ekstrak buah dicatatkan dengan hasil pengekstrakan (16.7g / 100g), TPC (78.63 mg GAE /g), TFC (5.79 mg RE / g) ABTS (54.8 mg trolox equiv / g) dan DPPH (127.3 mg trolox equiv /g) juga pada suhu pengekstrakan 180°C dan 90 minit. Selain itu, korelasi positif yang signifikan antara nilai TPC, TFC dan keupayaan antioksidan (DPPH dan ABTS) dikesan untuk kedua-dua ekstrak tersebut. Dalam ujian enzimatik, kedua-dua ekstrak menunjukkan perencatan positif yang signifikan ($p < 0.05$). Perencatan tertinggi oleh ekstrak akar dengan α-glukosidase (IC_{50} 2.72 ± 1.43 mg/ml), α-amilase (IC_{50} 0.31 ± 2.31 mg/ml), DPP (IV) (IC_{50} 3.9 ± 0.95 mg/ml) berbanding dengan ekstrak buah yang direkodkan dengan α-glukosidase (IC_{50} 5.6 ± 0.66 mg/ml) , α-amilase (IC_{50} 1.3 ± 0.75 mg/ml), DPP (IV) (IC_{50} 5.7 ± 0.66 mg/ml). Di samping itu, kedua-dua ekstrak tersebut menyebabkan peningkatan yang ketara ($p < 0.05$) dalam aktiviti pengambilan glukosa pada sel adiposit 3T3-L1 dan L6. Pengambilan glukosa tertinggi pada 3T3-L1 untuk akar dan ekstrak buah masing-masing adalah 67% dan 49%. Sementara itu, pengambilan glukosa tertinggi oleh sel otot L6 untuk ekstrak akar adalah 85% manakala untuk ekstrak buah adalah 68%. Selain itu, kedua ekstrak menunjukkan peningkatan yang signifikan ($p < 0.05$) dalam rembesan insulin dengan aktiviti tertinggi oleh akar dan buah masing-masing adalah 13.74 µg / ml dan 11.06 µg / ml pada garis BRIN-BD11cell pankreas. Hasil pemeriksaan saringan agonis ppar-γ menunjukkan ekstrak akar memberikan 25%, dan ekstrak buah memberikan 14% signifikan $p \leq 0.05$ dengan membandingkan kedua-dua ekstrak tersebut.Keputusan docking molekul menunjukkan phlorizin, scandenin, pomiferin dan mundulone dipilih sebagai perencat yang berpotensi dalam kebanyakan protein dengan mempunyai tenaga pengikat yang tertinggi dan beberapa ligan ini berinteraksi dengan sisa terpenting di kawasan tapak aktif protein. Kesimpulannya, kajian menunjukkan bahawa terdapat potensi yang terkandung di dalam *C. latifolia* sebagai agen alternatif terapeutik untuk pengurusan T2DM, terutama dengan memberi manfaat di dalam mekanisme utama T2DM.

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

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TABLE OF CONTENTS

	Page
ABSTRACT	i
ABSTRAK	iii
ACKNOWLEDGEMENTS	v
APPROVAL	vi
DECLARATION	viii
LIST OF TABLES	xiii
LIST OF FIGURES	xiv
LIST OF ABBREVIATIONS	xvi
LIST OF APPENDICES	xviii

CHAPTER

1	**INTRODUCTION**	1
	1.1 Background	1
	1.2 Objectives	4
	1.2.1 General objective	4
	1.2.2 Specific objectives	4
	1.3 Hypothesis	4
2	**LITERATURE REVIEW**	5
	2.1 Diabetes Mellitus: Definition and Classification	5
	2.1.1 Pathogenesis of Type 2 Diabetes Mellitus	6
	2.1.2 Epidemiology of Type 2 Diabetes Mellitus	7
	2.2 Management in Type 2 Diabetes Mellitus	8
	2.2.1 Physical Activity	8
	2.2.2 Dietary Therapy	9
	2.2.3 Pharmacological Treatment	9
	2.3 Targeted Organ in Treating Type 2 Diabetes Mellitus	10
	2.3.1 Pancreas	11
	2.3.1.1 Insulin Secretion	11
	2.3.1.2 Insulin Resistance (IR)	12
	2.3.2 Small Intestine	12
	2.3.2.1 Carbohydrate Mechanism	13
	2.3.2.2 Dipeptidyl Peptidase (IV) Mechanism	13
	2.3.3 Skeletal Muscle	14
	2.3.3.1 Glucose Uptake	14
	2.3.4 Adipose Tissue	15
	2.3.4.1 Peroxisome Proliferator-Activated Receptor (PPAR-γ) Agonist	16
	2.4 Antioxidant: Definition and Classification	16
	2.4.1 Antioxidant Assay	17
	2.4.2 Medicinal Plants as Potential Source of Antioxidant	17
	2.5 Plant Extraction of Antioxidant	18
	2.5.1 Subcritical Water Extraction (SWE)	19

2.6 Ethnopharmacology 20
2.6.1 Antidiabetic Activity of Medicinal Plant 20
2.6.2 *Curculigo latifolia* 21
2.6.3 *C. latifolia* as Type 2 Diabetes Mellitus Therapy 22
2.7 In-Silico Approach Towards Targeted Protein in Type 2 Diabetes Mellitus: Molecular Docking 23

3 METHODOLOGY 25
3.1 Plant Materials 25
3.2 Materials and Reagents 25
3.3 Subcritical Water Extraction (SWE) 25
3.4 Determination of Phytochemical Content 26
3.4.1 Determination Total Phenolic Content (TPC) 26
3.4.2 Determination of Total Flavonoid Content (TFC) 26
3.5 Determination of Antioxidant Activity 26
3.5.1 DPPH Free Radical Scavenging Activity 26
3.5.2 ABTS Radical Cation Scavenging Activity 27
3.6 Liquid Chromatography-Mass Spectrometry (LC-MS) analysis 27
3.7 Measurement of Enzymatic Inhibitory Activity 27
3.7.1 α-Glucosidase Inhibitory Assay 27
3.7.2 Mode of α-Glucosidase Inhibition 28
3.7.3 α-Amylase Inhibitory Assay 28
3.7.4 Mode of α-Amylase Inhibition 28
3.7.5 DPP (IV) Inhibitory Assay 29
3.8 *In Vitro* Studies 29
3.8.1 Cell Culture 29
3.8.2 Cell Cytotoxicity by MTT Assay 30
3.8.3 3T3-L1 Pre-Adipocyte Differentiation 30
3.8.4 2-NBDG Uptake Assay 30
3.8.5 Insulin Secretion Assay 31
3.8.6 PPAR-γ Agonist Assay 31
3.9 Molecular Docking 31
3.9.1 Preparation of Ligand 31
3.9.2 Preparation of Receptor 32
3.9.3 Docking Simulation 32
3.10 Statistical Analysis 32

4 RESULTS AND DISCUSSION 333
4.1 Influence of Subcritical Water Extraction (SWE) Variables on the Extraction Yield, TPC, TFC and Antioxidant Activity 333
4.1.1 Extraction Yield of *C. latifolia* Extracts 333
4.1.2 Total Phenolic Content (TPC) and Total Flavonoid Content (TFC) of *C. latifolia* 355
4.1.3 Antioxidant Activity of *C. latifolia* 388
4.2 Correlation between Antioxidant Activities and Phytochemical Content 41
4.3 Screening of Active Compound using LC-MS Analysis 42

4.4 Enzymatic Bioactivity Assay 45
4.4.1 α-Glucosidase Inhibitory Assay and Mode of Inhibition 455
4.4.2 α-Amylase Inhibitory Assay and Mode of Inhibition 49
4.4.3 DPP (IV) Inhibitory Assay 511
4.5 *In Vitro* Studies 533
4.5.1 Cell Viability Assessment in the Presence of *C. latifolia* Extract 533
4.5.2 Glucose Uptake Activity of *C. latifolia* Extract in 3T3-L1 Adipocyte and L6 Myotube Cell 544
4.5.3 Insulin Secretion Activity of *C. latifolia* Extract in BRIN-BD11 Pancreas Cell Line 577
4.5.4 PPAR-γ Agonist Assay 59
4.6 Molecular Docking Analysis 600

5 CONCLUSIONS AND RECOMMENDATIONS FOR FUTURE RESEARCH 711
5.1 Conclusions 711
5.2 Recommendations for future research 722

REFERENCES 733
APPENDICES 100
BIODATA OF STUDENT 111
LIST OF PUBLICATION 112

LIST OF TABLES

Table		Page
2.1	Example of Medicinal plants that has a beneficial effect in treating disease	18
4.1	Extraction yields of *C. latifolia* root and fruit extracts by subcritical water extraction (SWE) at different extraction conditions	34
4.2	Correlations between TPC, TFC, ABTS, DPPH of *C. latifolia's* extract	42
4.3	LC-MS analysis of *C. latifolia*	44
4.4	IC_{20} and IC_{50} values of *C. latifolia* root and fruit extract on 3T3-L1 preadipocytes, L6 muscle cell and BRIN-BD11 pancreatic cell	54
4.5	Molecular docking analysis	65
B1	Details for ligand interaction with α-amylase identifies by PLIP	102
B2	Details for ligand interaction with α-glucosidase identifies by PLIP	104
B3	Details for ligand interaction with DPP (IV) identifies by PLIP	106
B4	Details for ligand interaction with IR identifies by PLIP	108
B5	Details for ligand interaction with PPAR-γ identifies by PLIP	109

LIST OF FIGURES

Figure		Page
2.1	Comparison between Type 1 and Type 2 Diabetes Mellitus	6
2.2	Summarization of the pathogenesis in Type 2 Diabetes Mellitus	7
2.3	Prevalence (%) of people with diabetes by age and sex, 2019	8
2.4	Summarization targeted mechanism in the treatment of T2DM.	11
2.5	Glucose- stimulated insulin secretion by pancreatic β- cell	12
2.6	Overall mechanism in inhibition of DPP (IV) enzyme	14
2.7	Glucose uptake via insulin-stimulated by GLUT4 translocation in muscle cell	15
2.8	PPARγ transcriptional activation mechanism	16
2.9	Water phase diagram as a function of pressure and temperature	20
2.10	*Curculigo latifolia*	22
4.1	Total phenolic content	36
4.2	Total flavonoid content	37
4.3	Comparison of DPPH Scavenging activity	39
4.4	Comparison of ABTS Scavenging activity	40
4.5	LC-MS chromatogram screening of *C. Latifolia*	43
4.6	α-glucosidase inhibitory effects of the extracts and the acarbose reference as a positive control	46
4.7	Mode of inhibition of α-glucosidase by *C. latifolia* extract a) Michelis-Menten plot and b) Lineweaver-Burk plot	48
4.8	α-amylase inhibitory effects of the extracts and the acarbose as a positive control reference	50
4.9	Mode of inhibition of α-amylase by extract of *C. latifolia*	51

4.10	DPP (IV) inhibitory effects of the extracts and sitagliptin reference as a positive control	52
4.11	Microscopic images on lipid formation of randomly selected 3T3-L1 adipocytes on day 12 from red O staining	54
4.12	Percentage of glucose uptake after treatment with various concentration	55
4.13	Insulin secretion assay for root and fruit of *C. latifolia* extracts	58
4.14	PPAR-γ agonist assay for root and fruit of *C.latifolia* extracts with rosiglitazione as a reference control	59
4.15	Compounds from SWE of *C. latifolia* with potential antidiabetic activity selected for in silico studies	61
4.16	Active site in each targeted protein	62
4.17	Binding energy between targeted protein and ligand	64
4.18	Best docked of complex molecule with α-amylase enzyme	66
4.19	Best docked of complex molecule with α-glucosidase enzyme	66
4.20	Best docked of complex molecule with DPP (IV) enzyme	67
4.21	Best docked of complex molecule with IR protein	67
4.22	Best docked of complex molecule with PPAR-γ protein	68
A	Standard graph of pytochemical and antioxidant assay	101
C	MTT assay	111

LIST OF ABBREVIATIONS

2-NBDG	2-Deoxy-2-[(7-nitro-2,1,3-benzoxadiazol-4-yl)amino]-D-glucose
ABTS	2,2'-Azino-bis(3-ethylbenzothiazoline-6-sulphonic acid)
ANOVA	Analysis of variance
ATCC	American Type Culture Collection
$CaCl_2$	Calcium chloride
CO_2	Carbon dioxide
DMEM	Dulbecco's modified eagle's medium
DMSO	Dimethyl sulfoxide
DPP (IV)	Dipeptidyl peptidase (IV)
DPPH	2,2-diphenyl-1-picryl-hydrazyl-hydrate
EDTA	Ethylenediaminetetraacetic acid
FBS	Fetal bovine serum
FCS	Fetal calf serum
g	Gram
GAE	Gallic acid equivalent
GLP-1	Glucagon-like peptide 1
GLUT4	Glucose transporter type 4
HCl	Hydrochloric acid
HPLC-DAD	High-performance liquid chromatography with photodiode array detection
IBMX	3-Isobutyl-1-methylxanthine
IC_{20}	20 % Inhibitory concentration
IC_{50}	50 % Inhibitory concentration
IR	Insulin receptor
IRS	Insulin receptor substrate
KRP	Krebs Ringer Phosphate solution
LC-MS	Liquid chromatography mass spectrometry
M	Molarity
mg	Milligram

mL	Millilitre
mm	Millimetre
mM	Millimolar
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
N	Normality
Na_2CO_3	Sodium carbonate
NaCl	Sodium chloride
NaOH	Sodium hydroxide
nm	Nanometer
PBS	Phosphate-buffered saline
PDB	Protein Data Bank
pNA	paranitroanilide
pNPG	p-nitropheynyl glucopyranoside
QR	Quercetin equivalent
RE	Rutin equivalent
rpm	Revolutions per minute
Rt	Retention time
SWE	Subcritical water extraction
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TE	Trolox equivalent
TFC	Total flavonoid content
TPC	Total phenolic content
TZD	Thiazolidinedione
v/v	Volume per volume
w/v	Weight per volume

LIST OF APPENDICES

Appendix		Page
A	Standard graph of phtochemical and antioxidant assays	99
B	Binding interaction in molecular docking	101
C	Mtt assay	109

CHAPTER 1

INTRODUCTION

1.1 Background

Globally, diabetes mellitus (DM) is recognized as one of the major disease in the world with the highest crisis diseases in the 21st century (Okur *et al*., 2017). Nonetheless, the evolution of patients that suffering from diabetes has been increasing rapidly over the past year especially in most developing countries that experiencing an economic transformation, particularly from low to medium income (Zheng *et al*., 2014).

According to the International Diabetes Federation, 9th edition in 2019, it has been revealed that approximately 425 million adults between the ages of 20-79 years were diagnosed with diabetes. However, if this does not recover or reduced, this figure is expected to rise around 700 million by 2045. From the records, almost 49.7% was undiagnosed and living with diabetes (Cho *et al*., 2018). Globally, around 374 million people are at risk due to the development of type 2 diabetes mellitus (T2DM). Therefore, these occurred evolution is increasing awareness of people about T2DM (International Diabetes Federation, 2019). Additionally, the major causes of diabetes disease are mostly due to the unhealthy lifestyle factors, overweight (obesity), lack of exercise, smoking and some others (Zheng *et al*., 2014). According to National Health and Morbidity Survey in 2015, Malaysia also includes as one of the countries with a strong rise in diabetes and nearly 1.8 million out of 3.5 million among Malaysians diagnosed living with diabetes in these recent years.This record is the latest recorded data since the National Health and Morbidity Survey was conducted every 5 years. Therefore, an increasing trend in all the aspects give out diabetes disease as one of the most crucial and serious diseases to be treated.

Type 2 diabetes mellitus or shortly known as T2DM is a type of diabetes disease that has features of insulin resistance from the decrease in the peripheral glucose uptake in most of the targeted tissue. For T2DM, the cell becoming unresponsive towards insulin (Cersosimo *et al*., 2018). Heterogeneous metabolic disorders such as T2DM mainly caused by the inadequacy of insulin-producing β-cells to keep up with the demand. The resistance towards insulin occurring in peripheral tissues such as liver, muscle, and adipose tissues. In short, patient with T2DM are capable of producing insulin but becomes resistance and turns out to be ineffective (Okur *et al*., 2017). Due to the ongoing resistance to insulin, failure of pancreatic β-cell producing insulin and abnormality of insulin production are mostly leading to the production of high blood glucose in the body (Deepthi *et al*., 2017). Recently, the pathogenies of T2DM is intertwined with various type of mechanism such as increasing insulin secretion, insulin sensitivity, increased response towards incretin hormones, decreased absorption of glucose (Min *et al*., 2018). Therefore, several alternative techniques are required to control high blood glucose levels in T2DM patients. One of the most potent approaches in the management of T2DM is by delaying the absorption of sugar in the bloodstream that through an inhibitory potential of α-glucosidase and α-amylase enzyme, known as the main enzyme in the carbohydrate mechanism. The inhibitors of these enzymes are able to delay the absorption of monosaccharides from dietary complex carbohydrates, preventing any sudden rise in meal-induced blood glucose level (Oboh *et al*., 2014). Besides, Dipeptidyl peptidase (IV) inhibition also considered as a glucose-lowering treatment for T2DM. The overall mechanism for inhibition in DPP (IV) enzyme is to prevent the breakdown of Glucagon-like peptide (GLP-1) that responsible in lowering blood glucose level such as improving homeostasis of glucose by increasing insulin secretion and decreasing the secretion of glucagon (Min *et al*., 2018).

Besides from changes in diet or having healthy lifestyles, T2DM patient can be treat by consuming the antidiabetic oral drugs that act through with the varied mechanisms in terms to control the increased of glucose level. Clinically, there are several oral hyperglycemic drugs used to control this disease. These drugs are classified into different classes such as biguanides, sulfonylureas, thiazolidinediones (TZD), meglitinides, Dipeptidyl peptidase (IV) inhibitors, sodium-glucose cotransporter (SGLT2), and α-glucosidase inhibitors (Wang *et al*., 2018). Each of these classes of drug is targeting a different organ that are carried out in the various mode of action with undergoing different mechanisms. In addition, combinations of different antidiabetic drugs are typically used to increase the effectiveness of the medication (Gajbhiye *et al*., 2018). Given to their advantages, however, these medications also exert their own long-term effects such as cardiovascular disease, lactate acidosis, hypoglycemia, gastrointestinal symptoms, and others (Jiang *et al*., 2018). In light of that, some approaches in using medicinal plants have discovered as one of the alternative therapies in managing and preventing T2DM without any adverse effect (Gothai *et al*., 2016). Generally, these medicinal plants appeared to work in a dynamic way by targeting multiple receptor targets that can produce better therapeutic activity as antidiabetic agents (Telapolu *et al*., 2018).

Polyphenol is originally produced as plant origin secondary metabolites that are synthesized from L-phenylalanine or L-tyrosine through the phenylpropanoid pathway (Kallscheuer *et al*., 2017). The polyphenol that has been derived directly or indirectly from the plant is frequently implicated by having antidiabetic properties and plants have been discovered as a primary source of these natural drugs. Complementary studies have shown that polyphenol exerts a highly active compound that has a striking effects on human health and acts as a key mediator in lowering hyperglycemia (Dominguez *et al*., 2017). One example of polyphenol which is phenolic acids that commonly incorporated with other structures such as flavonoids are forming as a complex polyphenol (Habtemariam *et al*., 2014). Phenolic compounds derived from natural sources have been associated with health benefits because of their antioxidant properties. Several studies have shown that this natural antioxidant can be used to treat and prevent various diseases, including cancer, hypertension, inflammation, aging-related degenerative disorders, and diabetes mellitus. (Phoboo *et al*., 2015).

In this regards, antioxidant is characterized as any material that capable of preventing or delaying oxidative damage to a target molecule caused by overproduction of reactive oxygen species (ROS) above normal levels (Alimi *et al*., 2017). The mechanisms of action in antioxidants are divided into two classes, which are preventive and chain-breaking antioxidants that allow them to reduce and scavenge the radicals in order to alleviate the disease (Nimse *et al*., 2015). Plants that contain polyphenols such as phenolic acids, flavonoids, carotenoids, and vitamins are more likely to have high antioxidant activity that plays a key role in the body defense system. (Xu *et al*., 2017).

Locally known as lemba or lumbah, *Curculigo latifolia* (*C. latifolia*) is a stemless herb, which grows mostly in Western Malaysia and is categorized under family *Hypoxidaceae*. There are approximately 20 known species of *Curculigo*. Some of these species are said to have medicinal properties, such as acting as an anticancer agent and preventing gastrointestinal, cardiovascular and heart-related diseases (Hejazi *et al*., 2018). It is claimed that this plant has been traditionally used to treat high fever by using leaf and flower while the root can be used to ease stomach-ache and frequent urination (Farzinebrahimi *et al*., 2013). Besides, the fruits of *C. latifolia* have been used by the natives as a sweetener that exhibits taste modifying activities and traditionally been used for the treatment of antidiabetic, diuretic and urinary problems (Ishak *et al*., 2013). Interestingly, the sweet taste is derived from the isolated protein, the curculin in the *C. latifolia's* fruit may be one of the ways to address potential diabetes treatment (Farzinebrahimi *et al*., 2013). From the previous study, *C. latifolia* has been identified to exhibit antidiabetic properties through different cell lines and *in vivo* studies has shown to modulate glucose and lipid metabolism in experimental diabetic rats. The presence of curculigoside may have bestowed its antidiabetic efficacy (Ishak *et al*., 2013).

Root and fruit of *C. latifolia* were studied previously by having a potential in antidiabetic activity. Besides, previous studies reported that by increasing the concentration of root extracts, it improved the glucose tolerance and secretion of insulin through activated pathway that underlying with the mechanism of type 2 diabetes (Ooi *et al*., 2018). Hence, these additional studies may explore more in antidiabetic through other mechanisms that regulated in type 2 diabetes.However, the antidiabetic content was measured based on the basis of using solvent as the medium of extraction. This may cause several side effects from the toxicity of the solvents used. However, this present study proposed of using green technology extraction which is subcritical water extraction where use only water in the whole extraction process to produce great quality of the extracts. In addition, no previous studies have this plant on the inhibition of enzymes involved in the digestion of carbohydrate.Therefore, this studies included new explored antidiabetic mechanism in the digestion of carbohydrate, inhibition of DPP (IV) that generally relates to reduce glucose level. Besides, new findings can be made through a computational *in silico* studies in order to explore the binding interaction between the active compounds that found in *C. latifolia* with the protein involved in T2DM through a molecular docking. This new finding would provide new insight into the important basis for offering novel therapeutic options in the treatment and prevention of T2DM.

1.2 Objectives

1.2.1 General objective

To evaluate antioxidant by applying subcritical water extraction and antidiabetic properties of *Curculigo latifolia* through *in vitro* and molecular docking studies.

1.2.2 Specific objectives

1. To determine the optimum extraction temperature and time of *C. latifolia* by subcritical water extraction (SWE).
2. To examine the antioxidant activities of *C. latifolia* and screening of potentially bioactive compounds using liquid chromatography-mass spectrometry (LC-MS) analysis.
3. To investigate the antidiabetic activities of *C. latifolia* through *in vitro* studies.
4. To evaluate the binding affinities and interaction of different polyphenol from *C. latifolia* with α-glucosidase, α-amylase, DPP (IV), insulin receptor (IR) and PPAR-γ using molecular docking.

1.3 Hypothesis

1. Different extraction temperature and time will give the varied optimum extraction condition for *C. latifolia*.
2. Polyphenol rich in *C. latifolia* shows different antioxidant activities at various extraction temperature and time.
3. Polyphenol rich in *C. latifolia* extracts exhibit antidiabetic activity through *in vitro*.
4. The binding affinities and interaction of polyphenol compounds from *C. latifolia* varied at the different active side of α-glucosidase, α-amylase, DPP (IV), insulin receptor (IR) and PPAR-γ through molecular docking.

REFERENCES

Abbas, Q., Hassan, M., Raza, H., Kim, S. J., Chung, K. W., Kim, G. H., & Seo, S. Y. (2017). In vitro, in vivo and in silico anti-hyperglycemic inhibition by sinigrin. *Asian Pacific Journal of Tropical Medicine*, *10*(4), 372-379. https://doi.org/10.1016/j.apjtm.2017.03.019

Abdel-Raziq, M. S., Bar, F. M. A., & Gohar, A. A. (2016). Alpha-amylase inhibitory compounds from Musa cavendish. *British Journal of Pharmaceutical Research*, *13*(4), 1-10. https://doi.org/10.9734/BJPR/2016/29280

Abirami, N., Natarajan, B and Sagadevan, E. (2014). Phytochemical investigation and in vitro evaluation of hypoglycemic potential of Grewia Hirsuta, *International Journal of Pharma Bio Sciences*, *5*(1),76-83.

Adisakwattana, S. (2017). Cinnamic acid and its derivatives: mechanisms for prevention and management of diabetes and its complications. *Nutrients*, *9*(2), 163. https://doi.org/10.3390/nu9020163

Adisakwattana, S.; Hsu, W.H.; Yibchok-anun, S (2011). Mechanisms of p-methoxycinnamic acid-induced increase in insulin secretion. *Hormone and Metabolic Research*, 43, 766–773.

Aboulwafa, M. M., Youssef, F. S., Gad, H. A., Altyar, A. E., Al-Azizi, M. M., & Ashour, M. L. (2019). A Comprehensive insight on the health benefits and phytoconstituents of camellia sinensis and recent approaches for its quality control. *Antioxidants*, *8*(10), 455. https://doi.org/10.3390/antiox8100455

Ahmad, S., & Mittal, M. (2015). Diabetic Neuropathies. *JIMSA*, *28*(1), 51-53.

Ahmadian, M., Liu, S., Reilly, S. M., Hah, N., Fan, W., Yoshihara, E., & Dai, Y. (2018). ERRγ preserves brown fat innate thermogenic activity. *Cell reports*, *22*(11), 2849-2859. https://doi.org/10.1016/j.celrep.2018.02.061

Ahn, C. H., & Lim, S. (2019). Effects of thiazolidinedione and new antidiabetic agents on stroke. *Journal of Stroke*, *21*(2), 139-150.

Akbarirad, H., Ardabili, A. G., Kazemeini, S. M., & Khaneghah, A. M. (2016). An overview on some of important sources of natural antioxidants. *International Food Research Journal*, *23*(3), 928-933.

Alagesan, K., Raghupathi, P. K., & Sankarnarayanan, S. (2012). Amylase inhibitors: potential source of anti-diabetic drug discovery from medicinal plants. *International Journal of Pharmacy and Life Science*, *3*(2), 1407-1412.

Alam, F., Islam, A., Ibrahim Khalil, M., & Hua Gan, S. (2016). Metabolic control of type 2 diabetes by targeting the GLUT4 glucose transporter: intervention approaches. *Current Pharmaceutical Design*, *22*(20), 3034-3049.

Al-Dalaeen AM, AL-Domi HA (2018) Advanced glycation end products: Mechanisms in the pathogenesis of type 2 diabetes and its complications. *Journal of Research and Diabetes Metabolism*. *4*(1), 016- 020.

Alimi, A. A., & Ashafa, A. O. T. (2017). An in vitro evaluation of the antioxidant and antidiabetic potential of Sutherlandia montana E. Phillips & RA dyer leaf extracts. *Asian Pacific Journal of Tropical Biomedicine*, *7*(9), 765-772. https://doi.org/10.1016/j.apjtb.2017.08.004

Alisi, A., Pampanini, V., De Stefanis, C., Panera, N., Deodati, A., Nobili, V., & Cianfarani, S. (2018). Expression of insulin-like growth factor I and its receptor in the liver of children with biopsy-proven NAFLD. *Plos One*, *13*(7), e0201566.

Altemimi, A., Watson, D. G., Choudhary, R., Dasari, M. R., & Lightfoot, D. A. (2016). Ultrasound 276 assisted extraction of phenolic compounds from peaches and pumpkins.*Plos One,11*(2), 277. https://doi.org/10.1371/journal.pone.0148758

Alu'datt, M. H., Rababah, T., Sakandar, H. A., Imran, M., Mustafa, N., Alhamad, M. N., & Ayadi, W. (2018). Fermented food-derived bioactive compounds with anticarcinogenic properties: fermented royal jelly as a novel source for compounds with health benefits. *Properties and Application*, *1*, 141-165. https://doi.org/10.1007/978-981-10-8548-2_7

Alvim, R. O., Cheuhen, M. R., Machado, S. R., Sousa, A. G. P., & Santos, P. C. (2015). General aspects of muscle glucose uptake. *Anais da Academia Brasileira de Ciências*, *87*(1), 351-368. https://doi.org/10.1590/0001-3765201520140225

AL-Zuaidy, M. H., Ismail, A., Mohamed, S., Razis, A. F. A., Mumtaz, M. W., Hamid. (2018). Antidiabetic potential of Sutherlandia Montana E. Phillips & RA Dyer leaf extracts. *Asian Pacific Journal of Tropical Biomedicine*, *7*(9), 765-772.

American Diabetes Association. (2013). Diagnosis and classification of diabetes mellitus. *Diabetes care*, *36*(Supplement 1), S67-S74.

Apak, R., Özyürek, M., Güçlü, K., & Çapanoğlu, E. (2016). Antioxidant activity/capacity measurement. 1. classification, physicochemical principles, mechanisms, and electron transfer (ET)-based assays. *Journal of Agricultural and Food Chemistry*, *64*(5), 997-1027.

Arora, M., Kaur, G., Singh, S., Mahajan, A., & Sembi, J. K. (2017). TPC, TFC & antioxidant activities of Crepidium acuminatum (D. Don) Szlach. *Journal of Pharmacognosy and Phytochemistry*, *6*(4), 811-817.

Arulselvan, P., Ghofar, H. A. A., Karthivashan, G., Halim, M. F. A., Ghafar, M. S. A., & Fakurazi, S. (2014). Antidiabetic therapeutics from natural source: A systematic review. *Biomedicine and Preventive Nutrition*, *4*(4), 607-617. https://doi.org/10.1016/j.bionut.2014.07.009

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. https://dx.doi.org/10.4103%2F2277-9531.127541

Asokan, A., & Thangavel, M. (2014). In vitro cytotoxic studies of crude methanolic extract of Saraca indica bark extract. *IOSR Journal of Pharmacy and Biological Sciences*, *9*(4), 26-30.

Atanasov, A. G., Wang, J. N., Gu, S. P., Bu, J., Kramer, M. P., Baumgartner, L., & Noha, S. M. (2013). Honokiol: a non-adipogenic PPARγ agonist from nature. *Biochimica et Biophysica Acta (BBA)-General Subjects*, *1830*(10), 4813-4819.

Avery, L., Flynn, D., Van Wersch, A., Sniehotta, F. F., & Trenell, M. I. (2012). Changing physical activity behavior in type 2 diabetes: a systematic review and meta-analysis of behavioral interventions. *Diabetes Care*, *35*(12), 2681-2689.

Bahmani F, Tajadadi-Ebrahimi M, Kolahdooz F, Mazouchi M, Hadaegh H, Jamal AS (2016). The consumption of synbiotic bread containing Lactobacillus sporogenes and inulin affects nitric oxide and malondialdehyde in patients with type 2 diabetes mellitus: randomized, double blind. *Placebo-Controlled Trial. Journal of American College of the Nutrition*, *35*(6), 506-513.

Bajaj, H. S., Brown, R. E., Bhullar, L., Sohi, N., Kalra, S., & Aronson, R. (2018). SGLT2 inhibitors and incretin agents: associations with alanine aminotransferase activity in type 2 diabetes. *Diabetes and Metabolism*, *44*(6), 493-499.

Baldisserotto, A., Malisardi, G., Scalambra, E., Andreotti, E., Romagnoli, C., Vicentini, C., & Vertuani, S. (2012). Synthesis, antioxidant and antimicrobial activity of a new phloridzin derivative for dermo-cosmetic applications. *Molecules*, *17*(11), 13275-13289.

Baynes, H. W. (2015). Classification, pathophysiology, diagnosis and management of diabetes mellitus. *Journal Diabetes Metabolism*, *6*(5), 1-9.

Belwal, T., Dhyani, P., Bhatt, I. D., Rawal, R. S., & Pande, V. (2016). Optimization extraction conditions for improving phenolic content and antioxidant activity in Berberis asiatica fruits using response surface methodology (RSM). *Food Chemistry*, *207*, 115-124.

Bharti, S. K., Krishnan, S., Kumar, A., & Kumar, A. (2018). Antidiabetic phytoconstituents and their mode of action on metabolic pathways. *Therapeutic Advances in Endocrinology and Metabolism*, *9*(3), 81-100.

Bhardwaj, P., Thakur, M. S., Kapoor, S., Bhardwaj, A. K., Sharma, A., Saxena, S., & Chaurasia, O. P. (2019). Phytochemical screening and antioxidant activity study of methanol extract of stems and roots of Codonopsis clematidea from trans-himalayan Region. *Pharmacognosy Journal*, *11*(3), 536-546.

Boland, B. B., Rhodes, C. J., & Grimsby, J. S. (2017). The dynamic plasticity of insulin production in β-cells. *Molecular Metabolism*, *6*(9), 958-973.

Boucher J, Kleinridders A, Kahn CR. (2014) Insulin receptor signaling in normal and insulin resistant states. *Cold Spring Harb Perspect Biology*, *6*(1), a009191.

Brglez Mojzer, E., Knez Hrnčič, M., Škerget, M., Knez, Ž. & Bren, U. (2016). Polyphenols: extraction methods, antioxidative action, bioavailability and anticarcinogenic effects. *Molecules*, *21*(7), 901.

Bueschbell, B., Barreto, C. A., Preto, A. J., Schiedel, A. C., & Moreira, I. S. (2019). A complete assessment of dopamine receptor-ligand interactions through computational methods. *Molecules*, *24*(7), 1196.

Bugliani, M., Syed, F., Paula, F. M., Omar, B. A., Suleiman, M., Mossuto, S., & Filipponi, F. (2018). DPP-4 is expressed in human pancreatic beta cells and its direct inhibition improves beta cell function and survival in type 2 diabetes. *Molecular and Cellular Endocrinology*, *473*, 186-193.

Burgos-Morón, E., Abad-Jiménez, Z., Martínez de Marañón, A., Iannantuoni, F., Escribano-López, I., López-Domènech, S., & Solá, E. (2019). Relationship between oxidative stress, ER stress, and inflammation in type 2 diabetes: The battle continues. *Journal of Clinical Medicine*, *8*(9), 1385. https://doi.org/10.3390/jcm8091385

Burr, J. F., Rowan, C. P., Jamnik, V. K., & Riddell, M. C. (2010). The role of physical activity in type 2 diabetes prevention: physiological and practical perspectives. *The Physician and Sportsmedicine*, *38*(1), 72-82.

Carocho, M., & Ferreira, I. C. (2013). A review on antioxidants, prooxidants and related controversy: natural and synthetic compounds, screening and analysis methodologies and future perspectives. *Food and Chemical Toxicology*, *51*, 15-25.

Catalano, K. J., Maddux, B. A., Szary, J., Youngren, J. F., Goldfine, I. D., & Schaufele, F. (2014). Insulin resistance induced by hyperinsulinemia coincides with a persistent alteration at the insulin receptor tyrosine kinase domain. *Plos One*, *9*(9), e108693.

Cavatão de Freitas, T., Oliveira, R. J. D., Mendonça, R. J. D., Candido, P. A., Pereira, S., Lopes, L., & Pereira, C. A. (2019). Identification of bioactive compounds and analysis of inhibitory potential of the digestive enzymes from Syzygium sp. extracts. *Journal of Chemistry*, *2019*.

Cersosimo, E., Triplitt, C., Solis-Herrera, C., Mandarino, L. J., & DeFronzo, R. A. (2018). Pathogenesis of type 2 diabetes mellitus. In *Endotext [Internet]*.

Chakrabarti, R., Bhavtaran, S., Narendra, P., Varghese, N., Vanchhawng, L., Mohamed Sham Shihabudeen, H., & Thirumurgan, K. (2011). Dipeptidyl peptidase-IV inhibitory activity of Berberis aristata. *Journal of Natural Products*, *4*, 158-163.

Chakrabarti, S., Gilles, R. P., & Lazarova, E. (2018). Partial cooperation in strategic multi-sided decision situations. *Theory and Decision*, *85*(3-4), 455-478.

Chakraborty, C., Hsu, M. J., & Agoramoorthy, G. (2014). Understanding the molecular dynamics of type-2 diabetes drug target DPP-4 and its interaction with sitagliptin and inhibitor diprotin-A. *Cell Biochemistry and Biophysics*, *70*(2), 907-922.

Chaudhary, K. K., & Mishra, N. (2016). A review on molecular docking: Novel tool for drug discovery. *Databases*, *4*(3).1029.

Chaudhury, A., Duvoor, C., Dendi, R., Sena, V., Kraleti, S., Chada, A., & Kuriakose, K. (2017). Clinical review of antidiabetic drugs: Implications for type 2 diabetes mellitus management. *Frontiers in Endocrinology, 8*, 6. https://doi.org/10.3389/fendo.2017.00006

Cheigh, C. I., Yoo, S. Y., Ko, M. J., Chang, P. S., & Chung, M. S. (2015). Extraction characteristics of subcritical water depending on the number of hydroxyl group in flavonols. *Food Chemistry, 168*, 21-26.

Chikezie, P. C., Ibegbulem, C. O., & Mbagwu, F. N. (2015). Bioactive principles from medicinal plants. *Research Journal of Phytochemistry*, *9*(3), 88-115.

Chikezie, P. C., Ojiako, O. A., & Nwufo, K. C. (2015). Overview of antidiabetic medicinal plants: the Nigerian research experience. *Journal of Diabetes and Metabolism*, *6*(6), 546.

Chinnappan, S., Selvam, K., Sengottaiyan, A., Kamala, S., Selvankumar, T., & Govarthanan, M. (2017). Biomimetic synthesis of silver nanoparticles using flower extract of Bauhinia purpurea and its antibacterial activity against clinical pathogens. *Environmental Science and Pollution Research*, 25, 963-969.

Cho, N., Shaw, J. E., Karuranga, S., Huang, Y., da Rocha Fernandes, J. D., Ohlrogge, A. W., & Malanda, B. (2018). IDF Diabetes Atlas: Global estimates of diabetes prevalence for 2017 and projections for 2045. *Diabetes Research and Clinical Practice*, *138*, 271-281.

Choi, R. Y., Lee, H. I., Ham, J. R., Yee, S. T., Kang, K. Y., & Lee, M. K. (2018). Heshouwu (Polygonum multiflorum Thunb.) ethanol extract suppresses pre-adipocytes differentiation in 3T3-L1 cells and adiposity in obese mice. *Biomedicine and Pharmacotherapy*, *106*, 355-362.

Coelho, M., Oliveira, T., & Fernandes, R. (2013). Biochemistry of adipose tissue: an endocrine organ. *Archives of Medical Science: AMS*, *9*(2), 191-200. doi: 10.5114/aoms.2013.33181

Colberg, S. R., Sigal, R. J., Yardley, J. E., Riddell, M. C., Dunstan, D. W., Dempsey, P. C., & Tate, D. F. (2016). Physical activity/exercise and diabetes: a position statement of the American Diabetes Association. *Diabetes Care, 39*(11), 2065-2079. https://doi.org/10.2337/dc16-1728

Cvetanović, A., Švarc-Gajić, J., Gašić, U., Tešić, Ž. Zengin, G., Zeković, Z.,&Durovic S. (2017). Isolation of apigenin from subcritical water extracts: optimization of the process. *The Journal of Supercritical Fluids*, *120*, 32-42. https://doi.org/10.1016/j.supflu.2016.10.012

Cvetanović, A., Švarc-Gajić, J., Zeković, Z., Gašić, U., Tešić, Ž. Zengin, G. &Durovic S. (2018). Subcritical water extraction as an innovative technology for the extraction of bioactive compounds from chamomile: Influence of pressure on chemical composition and bioactivity of extracts. *Food Chemistry*, *266*, 389–396. https://doi.org/10.1016/j.foodchem.2018.06.037

Cvetanović, A., Zengin, G., Zeković, Z., Švarc-Gajić, J., Ražić, S., Damjanović, A., & Mitić, M. (2018). Comparative in vitro studies of the biological potential and chemical composition of stems, leaves and berries Aronia melanocarpa's extracts obtained by subcritical water extraction. *Food and Chemical Toxicology*, *121*, 458-466. https://doi.org/10.1016/j.fct.2018.09.045

Czech, M. P. (2017). Insulin action and resistance in obesity and type 2 diabetes. *Nature Medicine*, *23*(7), 804-814.

Da Cunha, J. D. S. M., Alfredo, T. M., dos Santos, J. M., Junior, V. V. A., Rabelo, L. A., Lima, E. S., & de Picoli Souza, K. (2018). Antioxidant, antihyperglycemic, and antidiabetic activity of Apis mellifera bee tea. *Plos One*, *13*(6), e0197071.

Dal, S., & Sigrist, S. (2016). The protective effect of antioxidants consumption on diabetes and vascular complications. *Diseases*, *4*(3),24. https://doi.org/10.3390/diseases4030024

De Ruyck, J., Brysbaert, G., Blossey, R., & Lensink, M. F. (2016). Molecular docking as a popular tool in drug design, an in silico travel. *Advances and Applications in Bioinformatics and Chemistry: AABC*, *9*, 1-11. https://dx.doi.org/10.2147%2FAABC.S105289

Deepthi, B., Sowjanya, K., Lidiya, B., Bhargavi, R. S., & Babu, P. S. (2017). A modern review of diabetes mellitus: an annihilatory metabolic disorder. *Journal of In Silico and In Vitro Pharmacology*, *3*(1), 1-14.

Defronzo, R. A., Ferrannini, E., Groop, L., Henry, R. R., Herman, W. H., Holst, J. J., & Simonson, D. C. (2015). Type 2 diabetes mellitus. *Nature Reviews Disease Primers*, *1*(1), 1-22. https://doi.org/10.1038/nrdp.2015.19

Deshmukh, A. S. (2016). Insulin-stimulated glucose uptake in healthy and insulin-resitant skeletal muscle. *Hormone Molecular Biology and Clinical Investigation*, *26*(1), 13-24. https://doi.org/10.1515/hmbci-2015-0041

Desseaux, V., Stocker, P., Brouant, P., & Ajandouz, E. H. (2018). The Mechanisms of alpha-amylase inhibition by Flavan-3-Ols and the possible impacts of drinking green tea on starch digestion. *Journal of Food Science*, *83*(11), 2858-2865. https://doi.org/10.1111/1750-3841.14353

Dixit, V. A., & Bharatam, P. V. (2013). SAR and computer-aided drug design approaches in the discovery of peroxisome proliferator-activated receptor γ activators: a perspective. *Journal of Computational Medicine*, *2013*. https://doi.org/10.1155/2013/406049

Domínguez Avila, J., Rodrigo García, J., González Aguilar, G., & de la Rosa, L.(2017)The antidiabetic mechanisms of polyphenols related to increased glucagon-like peptide-1 (GLP1) and insulin signaling. *Molecules*, *22*(6), 903. https://doi.org/10.3390/molecules22060903

Donaghue, K. C., Wadwa, R. P., Dimeglio, L. A., Wong, T. Y., Chiarelli, F., Marcove the, M. L. & Craig, M. E. (2014). Microvascular and macrovascular complications in children and adolescents. *Pediatric Diabetes*, *15*(S20), 257-269.

Dong B, Qi D, Yang L, Huang Y, Xiao X, Tai N, Wen L, Wong FS. (2012) TLR4 regulates cardiac lipid accumulation and diabetic heart disease in the nonobese diabetic mouse model of type 1 diabetes. *American Journal of Physiology Heart Circulatory Physiology*, *303*(6), 32–42. https://doi.org/10.1152/ajpheart.00948.2011

Douros, A., Dell'Aniello, S., Yu, O. H. Y., Filion, K. B., Azoulay, L., & Suissa, S. (2018). Sulfonylureas as second line drugs in type 2 diabetes and the risk of cardiovascular and hypoglycaemic events: population based cohort study. *Bmj*, *362*, k2693. https://doi.org/10.1136/bmj.k2693

Dudzińska, D., Boncler, M., & Watala, C. (2015). The cardioprotective power of leaves. *Archives of Medical Science: AMS*, *11*(4), 819-839. https://dx.doi.org/10.5114%2Faoms.2015.53303

Edgerton, D. S., Kraft, G., Smith, M., Farmer, B., Williams, P. E., Coate, K. C., & Cherrington, A. D. (2017). Insulin's direct hepatic effect explains the inhibition of glucose production caused by insulin secretion. *JCI insight*, *2*(6). e91863. https://dx.doi.org/10.1172%2Fjci.insight.91863

Egawa, T., Tsuda, S., Oshima, R., Goto, A., Ma, X., Goto, K., & Hayashi, T. (2017). Regulatory mechanism of skeletal muscle glucose transport by phenolic acids. *Phenolic compounds Biological Activities*, 169-191.

Elyasiyan, U., Nudel, A., Skalka, N., Rozenberg, K., Drori, E., Oppenheimer, R., & Rosenzweig, T. (2017). Anti-diabetic activity of aerial parts of Sarcopoterium spinosum. *BMC Complementary and Alternative Medicine*, *17*(1), 356. https://doi.org/10.1186/s12906-017-1860-7

Engwa, G. A. (2018). Free radicals and the role of plant phytochemicals as antioxidants against oxidative stress-related diseases. *Phytochemicals: Source of Antioxidants and Role in Disease Prevention*, 49-73.

Ersan, F., Üzengi Aktürk, O., Aktürk, E., & Ciraci, S. (2018). Metal–insulator transition and heterostructure formation by glycines self-assembled on defect-patterned graphene. *The Journal of Physical Chemistry C*, *122*(26), 14598-14605. https://doi.org/10.1021/acs.jpcc.8b03421

Escribano, O., Beneit, N., Rubio-Longás, C., López-Pastor, A. R., & Gómez-Harnandez, A. (2017). The Role of insulin receptor isoforms in diabetes and its metabolic and vascular complications. *Journal of Diabetes Research*, *2017*. https://doi.org/10.1155/2017/1403206

Esguerra, J., Mollet, I., Salunkhe, V., Wendt, A., & Eliasson, L. (2014). Regulation of pancreatic beta cell stimulus-secretion coupling by microRNAs. *Genes*, *5*(4), 1018-1031. https://doi.org/10.3390/genes5041018

Zamudio, J. D. C., Torres, M. D. P. N., Analco, J. A. G., & Laclette, E. I. (2019). Ethnopharmacological studies of Cecropia obtusifolia (Urticaceae) and importance in the treatment of type 2 diabetes mellitus: A mini-review. *Acta Botánic and Mexicana*, (126), 31.

Fakhruddin, S., Alanazi, W., & Jackson, K. E. (2017). Diabetes-induced reactive oxygen species: mechanism of their generation and role in renal injury. *Journal of Diabetes Research*, *2017*. https://doi.org/10.1155/2017/8379327

Fang Y, Wang S, Wu J et al (2017). The kinetics and mechanism of α-glucosidase inhibition by F5-SP, a novel compound derived from sericin peptides. *Food and Function*, 8(1), 323–332. https://doi.org/10.1039/C6FO01215A

Farzinebrahimi, R., Mat Taha, R., Rashid, K. A., Ali Ahmed, B., Danaee, M., &Rozali S. E. (2016).Preliminary screening of antioxidant and antibacterial activities and establishment of an efficient callus induction in Curculigo latifolia Dryand (Lemba). *Evidence-Based Complementary and Alternative Medicine*, *2016*. https://doi.org/10.1155/2016/6429652

Farzinebrahimi, R., Taha, R. M., & Rashid, K. A. (2013). Effect of light intensity and soil media on establishment and growth of Curculigo latifolia Dryand. *Journal of Applied Horticulture*, *15*(3), 224-226.

Fathima, H. M., Thangavelu, L., & Roy, A. (2018). Anti-diabetic activity of cassia fistula (alpha amylase–inhibitory effect). *Journal of Advanced Pharmacy Education and Research| Apr-Jun*, *8*(2), 13.

Fatima, M., Sadeeqa, S., & Nazir, S. U. (2018). Metformin and its gastrointestinal problems: A review. *Biomedical Research*, *29*(11), 2285-9.

Ferreira LG, Dos Santos RN, Oliva G, Andricopulo AD. Molecular docking and structure based drug design strategies. *Molecules*, *20*(7), 13384-13421.

Figueiredo-González, M., Reboredo-Rodríguez, P., González-Barreiro, C., Carrasco-Pancorbo, A., Cancho-Grande, B., & Simal-Gándara, J. (2018). The involvement of phenolic-rich extracts from Galician autochthonous extra-virgin olive oils against the α-glucosidase and α-amylase inhibition. *Food Research International*, *116*, 447-454.

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), 202-230. https://dx.doi.org/10.1900%2FRDS.2014.11.202

Forbes, J. M., & Cooper, M. E. (2013). Mechanisms of diabetic complication. Physio*logical Reviews*, *93*(1), 137-188. https://doi.org/10.1152/physrev.00045.2011

Frontera, A., Gamez, P., Mascal, M., Mooibroek, T. J., & Reedijk, J. (2011). Putting anion–π interactions into perspective. *Angewandte Chemie International Edition*, *50*(41), 9564-9583.

Fu, Z., R Gilbert, E., & Liu, D. (2013). Regulation of insulin synthesis and secretion and pancreatic Beta-cell dysfunction in diabetes. *Current Diabetes Reviews*, *9*(1), 25-53. https://doi.org/10.2174/157339913804143225

Gajbhiye RL, Ganapathy A, Jaisankar P. (2018). A review of alpha-glucosidase and alpha-amylase inhibitors for type 2 diabetes isolated from some important indian medicinal plants. *Annals of Clinical Pharmacology and Therapeutic*, 1(1), 1-10.

Garg, K., Tripathi, C. D., & Kumar, S. (2013). Clinical review of sitagliptin: a DPP-4 inhibitor. *Journal of the Association of Physicians of India*, *61*(9), 645-649.

Garry, E. M., Buse, J. B., Gokhale, M., Lund, J. L., Nielsen, M. E., Pate, V., & Stürmer, T. (2019). Study design choices for evaluating the comparative safety of diabetes medications: An evaluation of pioglitazone use and risk of bladder cancer in older US adults with type-2 diabetes. *Diabetes, Obesity and Metabolism*, *21*(9), 2096-2106.

Gastaldelli, A., & Cusi, K. (2019). From NASH to diabetes and from diabetes to NASH: Mechanisms and treatment options. *JHEP Reports*, *1*(4), 312-328. https://doi.org/10.1016/j.jhepr.2019.07.002

Gastaldelli, A., Gaggini, M., & DeFronzo, R. A. (2017). Role of adipose tissue insulin resistance in the natural history of type 2 diabetes: results from the San Antonio Metabolism Study. *Diabetes*, *66*(4), 815-822. https://doi.org/10.2337/db16-1167

Gbashi, S., Adebo, O. A., Piater, L., Madala, N. E., & Njobeh, P. B. (2017). Subcritical water extraction of biological materials. *Separation & Purification Reviews*, *46*(1), 21-34. https://doi.org/10.1080/15422119.2016.1170035

Ghorbani, M., Shiravi, A., Vaezi, G., Sepehri, H., Hojati, V., & Khori, V. (2019). A non-insulin herbal treatment to improve liver tissue in diabetic rats through gavage of walnut oil enriched with a phytosterol. *Cogent Biology*, *5*(1), 1648628.

Girgih, A. T., Udenigwe, C. C., & Aluko, R. E. (2011). In vitro antioxidant properties of hemp seed (Cannabis sativa L.) protein hydrolysate fractions. *Journal of the American Oil Chemists' Society*, 88, 381–389. https://doi.org/10.1007/s11746-010-1686-7

Girgis, C. M., Gunton, J. E., & Cheung, N. W. (2012). The influence of ethnicity on the development of type 2 diabetes mellitus in women with gestational diabetes: a prospective study and review of the literature. *ISRN endocrinology*, *2012*. https://doi.org/10.5402/2012/341638

Godinho, R., Mega, C., Teixeira-de-Lemos, E., Carvalho, E., Teixeira, F., Fernandes, R., & Reis, F. (2015). The place of dipeptidyl peptidase-4 inhibitors in type 2 diabetes therapeutics: a “me too” or “the special one” antidiabetic class. *Journal of Diabetes Research*, *2015*. https://doi.org/10.1155/2015/806979

Golmohammadi, M., Borghei, A., Zenouzi, A., Ashrafi, N., & Taherzadeh, M. J. (2018). Optimization of essential oil extraction from orange peels using steam explosion. *Heliyon*, *4*(11). https://doi.org/10.1016/j.heliyon.2018.e00893

González-Montoya, M., Hernández-Ledesma, B., Mora-Escobedo, R., & Martínez-Villaluenga, C. (2018). Bioactive Peptides from Germinated Soybean with Anti-Diabetic Potential by Inhibition of Dipeptidyl Peptidase-IV, α-Amylase, and α-Glucosidase Enzymes. *International Journal of Molecular Sciences*, *19*(10), 2883. https://doi.org/10.3390/ijms19102883

Gothai, S., Ganesan, P., Park, S. Y., Fakurazi, S., Choi, D. K., & Arulselvan, P. (2016). Natural phyto-bioactive compounds for the treatment of type 2 diabetes: inflammation as a target. *Nutrients*, *8*(8), 461.

Guardado-Sanchez, E., Brown, P. T., Mitra, D., Devakul, T., Huse, D. A., Schauß, P., & Bakr, W. S. (2018). Probing the quench dynamics of antiferromagnetic correlations in a 2D quantum Ising spin system. *Physical Review X*, *8*(2), 021069.

Guariguata, L., Whiting, D. R., Hambleton, I., Beagley, J., Linnenkamp, U., & Shaw, J. E. (2014). Global estimates of diabetes prevalence for 2013 and projections for 2035. *Diabetes Research and Clinical Practice*, *103*(2), 137-149. https://doi.org/10.1016/j.diabres.2013.11.002

Guerrero-Perilla, C., Bernal, F. A., & Coy-Barrera, E. D. (2015). Molecular docking study of naturallyoccurring compounds as inhibitors of N-myristoyl transferase towards antifungal agents discovery. *Revista Colombiana de Ciencias Químico-Farmacéuticas*, *44*(2), 162-178.

Gupta, D. K., Palma, J. M., & Corpas, F. J. (Eds.). (2018). Antioxidants and antioxidant enzymes in higher plants. *Springer*.

Gutiérrez-Rodelo, C., Roura-Guiberna, A., & Olivares-Reyes, J. A. (2017). Molecular mechanisms of insulin resistance: an update. *Gaceta medica de Mexico*, *153*(2), 214-228.

Habtemariam, S., & K Varghese, G. (2014). The antidiabetic therapeutic potential of dietary polyphenols. *Current Pharmaceutical Biotechnology*, *15*(4), 391-400.

Hackett, R. A., & Steptoe, A. (2017). Type 2 diabetes mellitus and psychologyical stress a modifiable risk factor. *Nature Reviews Endocrinology*, *13*(9), 547.

Haida, Z., & Hakiman, M. (2019). A comprehensive review on the determination of enzymatic assay and nonenzymatic antioxidant activities. *Food science and Nutrition*, *7*(5), 1555-1563. https://doi.org/10.1002/fsn3.1012

Handorf, A. M., Sollinger, H. W., & Alam, T. (2015). Insulin gene therapy for type 1 diabetes mellitus. *Experimental and Clinical Transplantation*, *13*(Suppl 1), 37-45.

Hardy, O. T., Czech, M. P., & Corvera, S. (2012). What causes the insulin resistance underlying obesity. *Current Opinion in Endocrinology, Diabetes, and Obesity*, *19*(2), 81-87. https://dx.doi.org/10.1097%FMED.0b013e3283514e13

Hassan, B. A. R. (2013). Overview on diabetes mellitus (type 2). *Chromatography Separation Techniques*, *4*(2), 144.

Hatting, M., Tavares, C. D., Sharabi, K., Rines, A. K., & Puigserver, P. (2018). Insulin regulation of gluconeogenesis. *Annals of the New York Academy of Sciences*, *1411*(1), 21-35. https://dx.doi.org/10.1111%2Fnyas.13435

He, L., Zhang, X., Xu, H., Xu, C., Yuan, F., Knez, Ž. & Gao, Y. (2012). Subcritical water extraction of phenolic compounds from pomegranate (Punica granatum L.) seed residues and investigation into their antioxidant activities with HPLC–ABTS+ assay. *Food and Bioproducts Processing*, *90*(2), 215-223. https://doi.org/10.1016/j.fbp.2011.03.003

Hejazi, I. I., Khanam, R., Mehdi, S. H., Bhat, A. R., Rizvi, M. M. A., Thakur, S. C., & Athar, F. (2018). Antioxidative and anti-proliferative potential of Curculigo orchioides Gaertn in oxidative stress induced cytotoxicity: In vitro, ex vivo and in silico studies. *Food and Chemical Toxicology*, *115*, 244-259. https://doi.org/10.1016/j.fct.2018.03.013

Holman, R.R.; Coleman, R.L.; Chan, J.C.N.; Chiasson, J.-L.; Feng, H.; Ge, J.; Gerstein ,H.C.; Gray, R.; Huo, Y.; Lang, Z.(2017). Effects of acarbose on cardiovascular and diabetes outcomes in patients with coronary heart disease and impaired glucose tolerance (ACE): A Randomised, Double-Blind, Placebo-Controlled Trial. *Lancet Diabetes Endocrinol*, *5* (11), 877–886. https://doi.org/10.1016/S2213-8587(17)30309-1

Holst, J. J., & Madsbad, S. (2016). Mechanisms of surgical control of type 2 diabetes: GLP-1 is key factor. *Surgery for Obesity and Related Diseases*, *12*(6), 1236-1242. https://doi.org/10.1016/j.soard.2016.02.033

Hong, P., Li, F. X., Gu, R. N., Fang, Y. Y., Lai, L. Y., Wang, Y. W., & Zhang, H. F. (2018). Inhibition of NLRP3 inflammasome ameliorates cerebral ischemia-reperfusion injury in diabetic mice. *Neural plasticity*, *2018*. https://doi.org/10.1155/2018/9163521

Huang, X., Liu, G., Guo, J., & Su, Z. (2018). The PI3K/AKT pathway in obesity and type 2 diabetes. *International Journal of Biological Sciences*, *14*(11), 1483-1496. https://dx.doi.org/10.7150%2Fijbs.27173

Hussein, Z., Taher, S. W., Singh, H. K. G., & Swee, W. C. S. (2015). Diabetes care in Malaysia: Problems, new models, and solutions. *Annals of Global Health*, *81*(6), 851-862. https://doi.org/10.1016/j.aogh.2015.12.016

Iannelli, P., Zarrilli, V., Varricchio, E., Tramontano, D., & Mancini, F. P. (2007). The dietary antioxidant resveratrol affects redox changes of PPARα activity. *Nutrition, Metabolism and Cardiovascular Diseases*, *17*(4), 247-256. https://doi.org/10.1016/j.numecd.2005.12.011

Ighodaro, O. M. (2018). Molecular pathways associated with oxidative stress in diabetes mellitus. *Biomedicine and Pharmacotherapy*, *108*, 656-662. https://doi.org/10.1016/j.biopha.2018.09.058

Ikpeazu, V. O., Igwe, K. K., & Otuokere, I. E. (2017). Binding energy predictions and molecular docking studies on 2-vinylbicyclo [2.1. 1] hex-2-ene, 3-methyl-6-hepten-1-ol and 2-ethyl-1-hexene steroidal receptors in Acalypha wilkesiana. *Journal of Environment and Life Sciences*, *2*(2), 58-65.

IS Sobczak, A., A Blindauer, C., & J Stewart, A. (2019). Changes in plasma free fatty acids associated with type-2 diabetes. *Nutrients*, *11*(9), 2022. https://doi.org/10.3390/nu11092022

Ishak, N. A., Ismail, M., Hamid, M., Ahmad, Z., & Abd Ghafar, S. A. (2013).Antidiabetic and hypolipidemic activities of curculigo latifolia fruit: root extract in high fat fed diet and low dose STZ induced diabetic rats. *Evidence-Based Complementary and Alternative Medicine, 2013*. https://doi.org/10.1155/2013/601838

J Meneses, M., M Silva, B., Sousa, M., Sa, R., F Oliveira, P., & G Alves, M. (2015). Antidiabetic drugs: Mechanisms of action and potential outcomes on cellular metabolism. *Current Pharmaceutical Design*, *21*(25), 3606-3620.

Jebur, A. B., Mokhamer, M. H., & El-Demerdash, F. M. (2016). A review on oxidative stress and role of antioxidants in diabetes mellitus. *Austin Endocrinal Diabetes Care Report*, *1*, 1006.

Jeon, M., Took, R. L., & Peters, G. L. (2018). A Clinical Overview of DPP-4 Inhibitors for Type 2 Diabetes. *Us Pharmacist*, *43*(10), 49-56.

Jhong, C. H., Riyaphan, J., Lin, S. H., Chia, Y. C., & Weng, C. F. (2015). Screening alpha-glucosidase and alpha-amylase inhibitors from natural compounds by molecular docking in silico. *BioFactors*, *41*(4), 242-251. https://doi.org/10.1002/biof.1219

Ji, W., Zhang,C., &Ji, H.(2017). Purification, identification andmolecular mechanism of two dipeptidyl peptidase IV (DPP-IV) inhibitory peptides from Antarctic krill (Euphausia superba) protein hydrolysate. *Journal of Chromotography B,1064*. 56-61. https://doi.org/10.1016/j.jchromb.2017.09.001

Jia, G., DeMarco, V. G., & Sowers, J. R. (2016). Insulin resistance and hyperinsulinaemia in diabetic cardiomyopathy. *Nature Reviews Endocrinology*, *12*(3), 144-153. https://doi.org/10.1038/nrendo.2015.216

Jiang, M., Yan, H., He, R., & Ma, Y. (2018). Purification and a molecular docking study of α-glucosidase-inhibitory peptides from a soybean protein hydrolysate with ultrasonic pretreatment. *European Food Research and Technology*, *244*(11), 1995-2005. https://doi.org/10.1007/s00217-018-3111-7

Jose, T., & Inzucchi, S. E. (2012). Cardiovascular effects of the DPP-4 inhibitor. Diab*abetes and Vascular Disease Research*, *9*(2), 109-116. https://doi.org/10.1177%2F1479164111436236

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

Kabel, A. M. (2017). Pharmacological Therapy of Type 2 Diabetes Mellitus: New Perspectives. *EC Pharmacology and Toxicology*, *4*, 12-19.

Kalita, D., Holm, D. G., LaBarbera, D. V., Petrash, J. M., & Jayanty, S. S. (2018). Inhibition of α-glucosidase, α-amylase, and aldose reductase by potato polyphenolic compounds. *Plos One*, *13*(1), e0191025.

Kallscheuer, N., Vogt, M.; Marienhagen, J. A Novel Synthetic Pathway Enables microbial Production of Polyphenols Independent from the Endogenous Aromatic Amino Acid Metabolism. *ACS Synthetic Biology*, 6, 410–415.

Kalra, S. (2014). Alpha glucosidase inhibitors. *JPMA. The Journal of the Pakistan Medical Association*, *64*(4), 474-476.

Kalra, S., Baruah, M. P., Sahay, R. K., Unnikrishnan, A. G., Uppal, S., & Adetunji, O. (2016). Glucagon-like peptide-1 receptor agonists in the treatment of type

2 diabetes: past, present, and future. *Indian Journal of Endocrinology and Metabolism*, *20*(2), 254.

Kaneto, H., Katakami, N., Matsuhisa, M., & Matsuoka, T. A. (2010). Role of reactive oxygen species in the progression of type 2 diabetes and atherosclerosis. *Mediators of Inflammation, 2010*. https://doi.org/10.1155/2010/453892

Kankeaw, U., & Masong, E. (2015). The antioxidant activity from hydroquinone derivatives by the synthesis of cinnamomium verum J. Presl bark's extracted. *International Journal of Chemical Engineering and Applications*, *6*(2), 91.

Kasote, D. M., Jayaprakasha, G. K., & Patil, B. S. (2018). Encapsulation of polyphenols: an effective way to enhance their bioavailability for gut health. In *Advances in Plant Phenolics: From Chemistry to Human Health*, 239-259.

Kasote, D. M., Katyare, S. S., Hegde, M. V., & Bae, H. (2015). Significance of antioxidant potential of plants and its relevance to therapeutic applications. *International Journal of Biological Sciences*, *11*(8), 982-991. https://dx.doi.org/10.7150%2Fijbs.12096

Kawamura, T., & Muraoka, I. (2018). Exercise-induced oxidative stress and the effects of antioxidant intake from a physiological viewpoint. *Antioxidants*, *7*(9), 119. https://doi.org/10.3390/antiox7090119

Kazeem, M. I., Ogunbiyi, J. V., & Ashafa, A. O. (2013). In vitro studies on the inhibition of α-Amylase and α-Glucosidase by leaf extracts of Picralima nitida (Stapf). *Tropical Journal of Pharmaceutical Research*, *12*(5), 719-725. https://doi.org/10.4314/tjpr.v12i5.9

Kempegowda, P. K., Zameer, F., Narasimashetty, C. K., Kollur, S. P., & Murari, S. K. (2018). Inhibitory potency of Withania somnifera extracts against DPP-4: an in vitro evaluation. *African Journal of Traditional, Complementary and Alternative Medicines*, *15*(1), 11-25.

Khan AN, Khan RA, Ahmad M, Mushtaq N. Role of antioxidant in oxidative stress and diabetes Mellitus. *Journal Pharmacognosy and Phytochemistry*, 3, 217-220.

Kiamahalleh, M. V. (2016). High performance curcumin subcritical water extraction from turmeric (Curcuma longa L.). *Journal of Chromatography B*, *1022*, 191-198. https://doi.org/10.1016/j.jchromb.2016.04.021

Kiamahalleh, M. V., Najafpour-Darzi, G., Rahimnejad, M., Moghadamnia, A. A., & Kim, Y., Keogh, J., & Clifton, P. (2016). Polyphenols and glycemic control. *Nutrients*, *8*(1), 17. https://doi.org/10.3390/nu8010017

Ko, M. J., Cheigh, C. I., Cho, S. W., & Chung, M. S. (2014). Subcritical water extraction offlavonol quercetin from onion skin. *Journal of Food Engineering*, *102*(4), 327-333.

Kooti, W., Farokhipour, M., Asadzadeh, Z., Ashtary-Larky, D., & Asadi-Samani, M. (2016). The role of medicinal plants in the treatment of diabetes: a systematic review. *Electronic Physician*, *8*(1), 1832-1842. https://dx.doi.or082%2F1832

Kopp, C., Singh, S., Regenhard, P., Müller, U., Sauerwein, H., & Mielenz, M. (2014). Trans-cinnamic acid increases adiponectin and the phosphorylation of AMP-activated protein kinase through G-protein-coupled receptor signaling in 3T3-L1 adipocytes. *International Journal of Molecular Sciences*, *15*(2), 2906-2915.

Krishnaiah, D., Sarbatly, R., Nithyanandam, R. (2011). A review of the antioxidant potential of medicinal plant species. *Food Bioproduction Process*. 89 (3), 217–233. https://doi.org/10.1016/j.fbp.2010.04.008

Kumar, S., Narwal, S., Kumar, V., & Prakash, O. (2011). α-glucosidase inhibitors from plants: A natural approach to treat diabetes. *Pharmacognosy Reviews*, *5*(9), 19-29. https://dx.doi.org/10.4103%2F0973-7847.79096

Kuppusamy, P., Lee, K. D., Song, C. E., Ilavenil, S., Srigopalram, S., Arasu, M. V., & Choi, K. C. (2018). Quantification of major phenolic and flavonoid markers in forage crop Lolium multiflorum using HPLC-DAD. *Revista Brasileira de Farmacognosia*, *28*(3), 282-288. https://doi.org/10.1016/j.bjp.2018.03.006

Kupsal, K., Mudigonda, S., Sai, N. V. B. K., Neelala, K., & Hanumanth, S. R. (2016). Metformin combinatorial therapy for type 2 diabetes mellitus. *Journal of Metabolic Syndrome*, *5*(210), 2167-0943.

Kurcinski, M., Oleniecki, T., Ciemny, M. P., Kuriata, A., Kolinski, A., & Kmiecik, S. (2018). CABS-flex standalone: a simulation environment for fast modeling of protein flexibility. *Bioinformatics*, *35*(4), 694-695. https://doi.org/10.1093/bioinformatics/bty685

Kwak, S. H., & Park, K. S. (2018). Pathophysiology of type 2 diabetes in koreans. *Endocrinology and Metabolism*, *33*(1), 9-16.

Lachos-Perez, D., Baseggio, A. M., Mayanga-Torres, P.C., Junior, M. R. M., Rostagno,M. A., Martínez, J., & Forster-Carneiro, T. (2018). Subcritical water extraction of flavanones from defatted orange peel. *The Journal of Supercritical Fluids*, *138*, 7-16. https://doi.org/10.1016/j.supflu.2018.03.015

Lafay, S., & Gil-Izquierdo, A. (2008). Bioavailability of phenolic acids. *Phytochemistry Reviews*, *7*(2), 301. https://doi.org/10.1007/s11101-007-9077-x

Lagani V, Koumakis L, Chiarugi F, Lakasing E, Tsamardinos I. A systematic review of predictive risk models for diabetes complications based on large scale clinical studies. *Journal Diabetes Complications*, *27*(4), 407–413. https://doi.org/10.1016/j.jdiacomp.2012.11.003

Laoufi, H., Benariba, N., Adjdir, S., & Djaziri, R. (2017). In vitro α-amylase and α-glucosidase inhibitory activity of Ononis angustissima extracts. *Journal Application Pharmaceutical Science*, *7*, 191-198.

Lee, J. H., Ko, M. J., & Chung, M. S. (2018). Subcritical water extraction of bioactive components from red ginseng (Panax ginseng CA Meyer). *The Journal of Supercritical Fluids*, *133*, 177-183. https://doi.org/10.1016/j.supflu.2017.09.029

Lee, J. H., Park, K. H., Lee, M. H., Kim, H. T., Seo, W. D., Kim, J. Y., & Ha, T. J. (2013). Identification, characterisation, and quantification of phenolic compounds in the antioxidant activity-containing fraction from the seeds of Korean perilla (Perilla frutescens) cultivars. *Food Chemistry*, *136*(2), 843-852.

Lee, M. T., Lin, W. C., Yu, B., & Lee, T. T. (2017). Antioxidant capacity of phytochemicals and their potential effects on oxidative status in animals—A review. *Asian-Australasian Journal of Animal Sciences*, *30*(3), 299-308. https://dx.doi.org/10.5713%2Fajas.16.0438

Les, F., Arbonés-Mainar, J. M., Valero, M. S., & López, V. (2018). Pomegranate polyphenols and urolithin A inhibit α-glucosidase, dipeptidyl peptidase-4, lipase, triglyceride accumulation and adipogenesis related genes in 3T3-L1 adipocyte-like cells. *Journal of Ethnopharmacology*, *220*, 67-74. https://doi.org/10.1016/j.jep.2018.03.029

Leto D, Saltiel AR. 2012. Regulation of glucose transport by insulin: traffic control of GLUT4. *Nature Review Molecular Cell Biology*, 13, 383–396. https://doi.org/10.1038/nrm3351

Li, H., Lin, L., Feng, Y., Zhao, M., Li, X., Zhu, Q., & Xiao, Z. (2018). Enrichment of antioxidants from soy sauce using macroporous resin and identification of 4-ethylguaiacol, catechol, daidzein, and 4-ethylphenol as key small molecule antioxidants in soy sauce. *Food Chemistry*, *240*, 885-892. https://doi.org/10.1016/j.foodchem.2017.08.001

Li, X., Chen, B., Xie, H., He, Y., Zhong, D., & Chen, D. (2018). Antioxidant structure–activity relationship analysis of five dihydrochalcones. *Molecules*, *23*(5), 1162.

Liao, F., Meng, Y., Zheng, H., He, D., Shen, X., Yu, J.,& Wang, L. (2018). Biospecific isolation and characterization of angiogenesis-promoting ingredients in Buyang Huanwu decoction using affinity chromatography on rat brain microvascular endothelial cells combined with solid-phase extraction, and HPLC-MS/MS. *Talanta*, *179*, 490-500. https://doi.org/10.1016/j.talanta.2017.11.018

Liguori, I., Russo, G., Curcio, F., Bulli, G., Aran, L., Della-Morte, D., & Abete, P. (2018). Oxidative stress, aging, and diseases. *Clinical Interventions in Aging*, *13*, 757-772. https://dx.doi.org/10.2147%2FCIA.S158513

Lin, S. R., Chang, C. H., Tsai, M. J., Cheng, H., Chen, J. C., Leong, M. K., & Weng, C. F. (2019). The perceptions of natural compounds against dipeptidyl peptidase 4 in diabetes: from in silico to in vivo. *Therapeutic Advances in Chronic Disease*, *10*. https://doi.org/10.1177%2F2040622319875305

Liu, X., Jia, L., Gao, Y., Tu, Y., 2014. Anti-inflammatory activity of total flavonoids from seeds of Camellia oleifera Abel. *Acta Biochimica Biophysica Sinica*, *46*(10), 920–922. https://doi.org/10.1093/abbs/gmu071

Long, W., & Cheeseman, C. I. (2015). Structure of, and functional insight into the GLUT family of membrane transporters. *Cell Health and Cytoskeleton*, *7*, 167-183. DOI:10.2147/CHC.S60484

Luni, C., Marth, J. D., & Doyle III, F. J. (2012). Computational modeling of glucose transport in pancreatic β-cells identifies metabolic thresholds and therapeutic targets in diabetes. *PloS one*, *7*(12), e53130.

Luong D, Sephton MA, Watson JS (2015). Subcritical water extraction of organic matter from sedimentary rocks. *Analytica Chimica Acta*, *879*,48- 57. https://doi.org/10.1016/j.aca.2015.04.027

Luong, N. Q., & Popescu-Belis, A. (2016). A contextual language model to improve machine translation of pronouns by re-ranking translation hypotheses. In *Proceedings of the 19th Annual Conference of the European Association for Machine Translation*, 292-304.

M. I. Kazeem, J. O. Adamson, and I. A. Ogunwande. (2013). Modes of Inhibition of α-amylase and α-Glucosidase by Aqueous Extract of Morinda lucida Benth Leaf. *BioMed Research International*, *2013*. https://doi.org/10.1155/2013/527570

Mamun-or-Rashid, A. N. M., Hossain, M. S., Hassan, N., Dash, B. K., Sapon, M. A., & Sen, M. K. (2014). A review on medicinal plants with antidiabetic activity. *Journal of Pharmacognosy and Phytochemistry*, *3*(4), 149-159.

Maori, L., Ezekiel, D., & Bilal, J. (2012). Prevalence of diabetes in zambuk general hospital. *Rep Opinion*, *4*, 54-57.

Mathebula, S. D. (2015). Polyol pathway: A possible mechanism of diabetes complications in the eye. *African Vision and Eye Health*, *74*(1), 5. https://doi.org/10.4102/aveh.v74i1.13

Meduru, H., Wang, Y. T., Tsai, J. J., & Chen, Y. C. (2016). Finding a potential dipeptidyl peptidase-4 (DPP-4) inhibitor for type-2 diabetes treatment based on molecular docking, pharmacophore generation, and molecular dynamics simulation. *International Journal of Molecular Sciences*, *17*(6), 920. https://doi.org/10.3390/ijms17060920

Mehta, S. K., & Gowder, S. J. T. (2015). Members of antioxidant machinery and their functions. *Basic Principles and Clinical Significance of Oxidative Stress*, 59-85.

Metwally, A. M., Radi, A. A., El-Shazoly, R. M., & Hamada, A. M. (2018). The role of calcium, silicon and salicylic acid treatment in protection of canola plants against boron toxicity stress. *Journal of Plant Research*, *131*(6), 1015-1028. https://doi.org/10.1007/s10265-018-1008-y

Min, S. H., Yoon, J. H., Moon, S. J., Hahn, S., & Cho, Y. M. (2018). Combination of sodium-glucose cotransporter 2 inhibitor and dipeptidyl peptidase-4 inhibitor in type 2 diabetes: a systematic review with meta-analysis. *Scientific Reports*, *8*(1), 4466. https://doi.org/10.1038/s41598-018-22658-2

Mishriky, B. M., Cummings, D. M., & Tanenberg, R. J. (2015). The efficacy and safety of DPP4 inhibitors compared to sulfonylureas as add-on therapy to metformin in patients with Type 2 diabetes: A systematic review and meta-analysis. *Diabetes Research and Clinical Practice*, *109*(2), 378–388. https://doi.org/10.1016/j.diabres.2015.05.025

Mohammed, A., Koorbanally, N. A., & Islam, M. S. (2015). Ethyl acetate fraction of Aframomum melegueta fruit ameliorates pancreatic β-cell dysfunction and major diabetes-related parameters in a type 2 diabetes model of rats. *Journal of Ethnopharmacology*, *175*, 518-527. https://doi.org/10.1016/j.jep.2015.10.011

Moharram, H. A., & Youssef, M. M. (2014). Methods for determining the antioxidant activity: a review. *Alexandria Journal of Food Science and Technology*, *11*(1), 31-42.

Møller, A. B., Kampmann, U., Hedegaard, J., Thorsen, K., Nordentoft, I., Vendelbo, M. H., & Jessen, N. (2017). Altered gene expression and repressed markers of autophagy in skeletal muscle of insulin resistant patients with type 2 diabetes. *Scientific Reports*, *7*, 43775. https://doi.org/10.1038/srep43775

Moradi, B., Abbaszadeh, S., Shahsavari, S., Alizadeh, M., & Beyranvand, F. (2018). The most useful medicinal herbs to treat diabetes. *Biomedical Research and Therapy*, *5*(8), 2538-2551.

Mujeeb, F., Bajpai, P., & Pathak, N. (2014). Phytochemical evaluation, antimicrobial activity, and determination of bioactive components from leaves of Aegle marmelos. *BioMed Research International*, *2014*. https://doi.org/10.1155/2014/497606

Mukesh, B., & Rakesh, K. (2011). Molecular docking: a review. *International Journal of Research in Ayurveda and Pharmacy*, *2*(6), 1746-1751.

Muralikumar, S., Vetrivel, U., Narayanasamy, A., & Das, U. N. (2017). Probing the intermolecular interactions of PPARγ-LBD with polyunsaturated fatty acids and their anti-inflammatory metabolites to infer most potential binding moieties. *Lipids in Health and Disease*, *16*(1), 17. https://doi.org/10.1186/s12944-016-0404-3

Nair, A.S.; Kavrekar, V.; Mishra. (2013). In vitro studies on Alpha amylase and Alpha Glucosidase inhibitory activities of selected plant extracts. *European Journal of Experimantal Biology*. 3, 128–132.

Narasimhan, B., Belsare, D., Pharande, D., Mourya, V., & Dhake, A. (2004). Esters, amides and substituted derivatives of cinnamic acid: synthesis, antimicrobial activity and QSAR investigations. *European Journal of Medicinal Chemistry*, *39*(10), 827-834. https://doi.org/10.1016/j.ejmech.2004.06.013

Navale, A. M., & Paranjape, A. N. (2016). Glucose transporters: physiological and pathological roles. *Biophysical Reviews*, *8*(1), 5-9. https://doi.org/10.1007/s12551-015-0186-2

Nimse, S. B., & Pal, D. (2015). Free radicals, natural antioxidants, and their reaction mechanisms. *Rsc Advances*, *5*(35), 27986-28006.

Noolu, B., Ajumeera, R., Chauhan, A., Nagalla, B., Manchala, R., & Ismail, A. (2013). Murraya koenigii leaf extract inhibits proteasome activity and induces cell death in breast cancer cells. *BMC Complementary and Alternative Medicine*, *13*(1), 7. https://doi.org/10.1186/1472-6882-13-7

Noor, A., Gunasekaran, S., & Vijayalakshmi, M. A. (2017). Improvement of insulin secretion and pancreatic β-cell function in streptozotocin-induced diabetic rats treated with Aloe vera extract. *Pharmacognosy Research*, *9*(Suppl 1), S99-S104. https://dx.doi.org/10.4103%2Fpr.pr_75_17

Oboh, G., Ademiluyi, A. O., Akinyemi, A. J., Henle, T., Saliu, J. A., & Schwarzenbolz, U. (2012). Inhibitory effect of polyphenol-rich extracts of jute leaf (Corchorus olitorius) on key enzyme linked to type 2 diabetes (α-amylase and α-glucosidase) and hypertension (angiotensin I converting) in vitro. *Journal of Functional Foods*, *4*(2), 450-458. https://doi.org/10.1016/j.jff.2012.02.003

Oboh, G., Isaac, A. T., Akinyemi, A. J., & Ajani, R. A. (2014). Inhibition of key enzymes linked to type 2 diabetes and sodium nitroprusside induced lipid peroxidation in rats' pancreas by phenolic extracts of avocado pear leaves and fruit. *International journal of Biomedical Science: IJBS*, *10*(3), 208-216.

Oyedemi, S. O., Oyedemi, B. O., Ijeh, I. I., Ohanyerem, P. E., Coopoosamy, R. M., & Aiyegoro, O. A. (2017). Alpha-amylase inhibition and antioxidative capacity of some antidiabetic plants used by the traditional healers in Southeastern Nigeria. *The Scientific World Journal*, *2017*. https://doi.org/10.1155/2017/3592491

Odeyemi, O. A., Burke, C. M., Bolch, C. C., & Stanley, R. (2018). Seafood spoilage microbiota and associated volatile organic compounds at different storage temperatures and packaging conditions. *International Journal of Food Microbiology*, *280*, 87-99. https://doi.org/10.1016/j.ijfoodmicro.2017.12.029

Odeyemi, S. W., & Afolayan, A. J. (2018). Identification of antidiabetic compounds from polyphenolic-rich fractions of Bulbine abyssinica A. rich leaves. *Pharmacognosy Research*, *10*(1), 72-80.

Okur, M. E., Karantas, I. D., & Siafaka, P. I. (2017). Diabetes Mellitus: a review on pathophysiology, current status of oral pathophysiology, current status of oral medications and future perspectives. *ACTA Pharmaceutica Sciencia*, *55*(1).

Olokoba, A. B., Obateru, O. A., & Olokoba, L. B. (2012). Type 2 diabetes mellitus: a review of current trends. *Oman Medical Journal*, *27*(4), 269-273. https://dx.doi.org/10.5001%2Fomj.2012.68

Ooi, D. J., Chan, K. W., Ismail, N., Imam, M. U., & Ismail, M. (2018). Polyphenol rich ethyl acetate fraction of Molineria latifolia rhizome restores oxidant-antioxidant balance by possible engagement of KEAP1-NRF2 and PKC/NF-κB signalling pathways. *Journal of Functional Foods*, *42*, 111-121. https://doi.org/10.1016/j.jff.2017.11.044

Ormazabal, V., Nair, S., Elfeky, O., Aguayo, C., Salomon, C., & Zuñiga, F. A. (2018). Association between insulin resistance and the development of cardiovascular disease. *Cardiovascular Diabetology, 17*(1), 122. https://doi.org/10.1186/s12933-018-0762-4

Ouassou, H., Zahidi, T., Bouknana, S., Bouhrim, M., Mekhfi, H., Ziyyat, A., & Bnouham, M. (2018). Inhibition of α-Glucosidase, Intestinal Glucose Absorption, and Antidiabetic Properties by Caralluma europaea. *Evidence-Based Complementary and Alternative Medicine*, *2018*. https://doi.org/10.1155/2018/9589472

Oyedemi, S. O., Oyedemi, B. O., Ijeh, I. I., Ohanyerem, P. E., Coopoosamy, R. M., & Aiyegoro, O. A. (2017). Alpha-amylase inhibition and antioxidative capacity of some antidiabetic plants used by the traditional healers in Southeastern Nigeria. *The Scientific World Journal*, *2017*. https://doi.org/10.1155/2017/3592491

Pal, J., Raju, C. V., Shukla, B. N., Verma, H. O., Pandey, G., Maurya, A. K., & Prasad, L. (2018). In-vitro antioxidant activity of freeze dried extracts fruit peel waste (Punica granatum and Citrus sinensis) and its effect in α-linoleic acid model system. *IJCS*, *6*(2), 892-895.

Panchal, S. K., Poudyal, H., & Brown, L. (2012). Quercetin Ameliorates Cardiovascular, Hepatic, and Metabolic Changes in Diet-Induced Metabolic Syndrome in Rats–. *The Journal of Nutrition*, *142*(6), 1026-1032.

Pantsar, T., & Poso, A. (2018). Binding Affinity via Docking: Fact and Fiction. *Molecules, 23*(8), 1899. https://doi.org/10.3390/molecules23081899

Pappachan, J. M., Chacko, E. C., Arunagirinathan, G., & Sriraman, R. (2011). Management of hypertension and diabetes in obesity: non-pharmacological measures. *International Journal of Hypertension*, *2011*.

Patel, R. P., & Barnes, S. (2010). Isoflavones and PPAR signaling: a critical target in cardiovascular, metastatic, and metabolic disease. *PPAR research*, *2010*. https://doi.org/10.1155/2010/153252

Pearson, T., Wattis, J. A., King, J. R., MacDonald, I. A., & Mazzatti, D. J. (2016). The effects of insulin resistance on individual tissues: an application of a mathematical model of metabolism in humans. *Bulletin of Mathematical Biology*, *78*(6), 1189-1217. https://doi.org/10.1007/s11538-016-0181-1

Phoboo, Susanna; Kalidas Shetty; and Tahra ElObeid. (2015). In Vitro Assays of Antidiabetic and Anti-hypertensive Potential of Some Traditional Edible Plants of Qatar. *Journal of Medicinally Active Plants*, *4* (3), 22-29. https://doi.org/10.7275/R59P2ZK6

Picard, M. & Turnbull, D. M. (2013). Linking the metabolic state and mitochondrial dna in chronic disease, health, and aging. *Diabetes*, *62*(3), 672–678. https://doi.org/10.2337/db12-1203

Pitocco, D., Tesauro, M., Alessandro, R., Ghirlanda, G., & Cardillo, C. (2013). Oxidative stress in diabetes: implications for vascular and other complications. *International Journal of Molecular Sciences*, *14*(11), 21525-21550. https://doi.org/10.3390/ijms141121525

Pizzino, G., Irrera, N., Cucinotta, M., Pallio, G., Mannino, F., Arcoraci, V., & Bitto, A. (2017). Oxidative stress: harms and benefits for human health. *Oxidative Medicine and Cellular Longevity*, *2017*.

Plows, J. F., Stanley, J. L., Baker, P. N., Reynolds, C. M., & Vickers, M. H. (2018). The pathophysiology of gestational diabetes mellitus. *International Journal of Molecular Sciences*, *19*(11), 3342. https://doi.org/10.3390/ijms19113342

Porskjær Christensen, L., & Bahij El-Houri, R. (2018). Development of an in vitro screening platform for the identification of partial PPARγ agonists as a source for antidiabetic lead compounds. *Molecules*, *23*(10), 2431. https://doi.org/10.3390/molecules23102431

Porskjær Christensen, L., & Bahij El-Houri, R. (2018). Development of an in vitro screening platform for the identification of partial PPARγ agonists as a source for antidiabetic lead compounds. *Molecules*, *23*(10), 2431.

Prasatha, G. S., Rahinia, S., Srinivasana, P. T., & Subramanianb, S. (2016). In vitro antioxidant and glucose uptake potential of Tinospora cordifolia leaves extract. *Der Pharmacia Lettre*, *8*, 132-139.

Proença, C., Freitas, M., Ribeiro, D., Tomé, S. M., Oliveira, E. F., Viegas, M. F., & Fernandes, E. (2019). Evaluation of a flavonoids library for inhibition of pancreatic α-amylase towards a structure–activity relationship. *Journal of Enzyme Inhibition and Medicinal Chemistry*, *34*(1), 577-588. https://doi.org/10.1080/14756366.2018.1558221

Qaid, M. M., & Abdelrahman, M. M. (2016). Role of insulin and other related hormones in energy metabolism—A review. *Cogent Food and Agriculture*, *2*(1), 1267691. https://doi.org/10.1080/23311932.2016.1267691

Rahim, F., Ullah, H., Javid, M. T., Wadood, A., Taha, M., Ashraf, M., & Mehmood, R. (2015). Synthesis, in vitro evaluation and molecular docking studies of thiazole derivatives as new inhibitors of α-glucosidase. *Bioorganic Chemistry*, *62*, 15-21. https://doi.org/10.1016/j.bioorg.2015.06.006

Rahimi-Madiseh, M., Malekpour-Tehrani, A., Bahmani, M., & Rafieian-Kopaei, M. (2016). The research and development on the antioxidants in prevention of diabetic complications. *Asian Pacific Journal of Tropical Medicine*, *9*(9), 825-831.

Reddy Peasari, J., sri Motamarry, S., Varma, K. S., Anitha, P., & Potti, R. B. (2018). Chromatographic analysis of phytochemicals in Costus igneus and computational studies of flavonoids. *Informatics in Medicine Unlocked*, *13*, 34-40. https://doi.org/10.1016/j.imu.2018.10.004

Rehman, A., Setter, S. M., & Vue, M. H. (2011). Drug-induced glucose alterations part 2: drug-induced hyperglycemia. *Diabetes Spectrum*, *24*(4), 234-238. https://doi.org/10.2337/diaspect.24.4.234

Ribeiro Filho, H. V., Bernardi Videira, N., Bridi, A. V., Tittanegro, T. H., Batista, H., Aparecida, F., & Figueira, A. C. M. (2018). Screening for PPAR Non-Agonist Ligands Followed by Characterization of a Hit, AM-879, with Additional No-Adipogenic and cdk5-Mediated Phosphorylation Inhibition Properties. *Frontiers in Endocrinology, 9*, 11. https://doi.org/10.3389/fendo.2018.00011

Roby, M. H. H., Sarhan, M. A., Selim, K. A. H., & Khalel, K. I. (2013). Evaluation of antioxidant activity, total phenols and phenolic compounds in thyme (Thymus vulgaris L.), sage (Salvia officinalis L.), and marjoram (Origanum majorana L.) extracts. *Industrial Crops and Products*, *43*, 827-831.

Röder, P. V., Wu, B., Liu, Y., & Han, W. (2016). Pancreatic regulation of glucose homeostasis. *Experimental and Molecular Medicine*, *48*(3), e219. https://doi.org/10.1038/emm.2016.6

Röhrborn, D., Wronkowitz, N., & Eckel, J. (2015). DPP4 in diabetes. *Frontiers in Immunology*, *6*, 386. https://doi.org/10.3389/fimmu.2015.00386

Rouzbehan, S., Moein, S., Homaei, A., & Moein, M. R. (2017). Kinetics of α-glucosidase inhibition by different fractions of three species of Labiatae extracts: a new diabetes treatment model. *Pharmaceutical Biology*, *55*(1), 1483-1488. https://doi.org/10.1080/13880209.2017.1306569

S. Oyedemi, T. Koekemoer, G. Bradley, M. Van De Venter, and A. Afolayan. (2013). In vitro anti-hyperglycemia properties of the aqueous stem bark extract from Strychnos henningsii (Gilg), *International Journal of Diabetes in Developing Countries*, 33(2), 120–127.

Saeedi, M., Mohammadi-Khanaposhtani, M., Pourrabia, P., Razzaghi, N., Ghadimi, R., Imanparast, S., & Rastegar, H. (2019). Design and synthesis of novel quinazolinone-1, 2, 3-triazole hybrids as new anti-diabetic agents: In vitro α-glucosidase inhibition, kinetic, and docking study. *Bioorganic Chemistry*, *83*, 161-169. https://doi.org/10.1016/j.bioorg.2018.10.023

Sales, P. M., Souza, P. M., Simeoni, L. A., Magalhães, P. O., & Silveira, D. (2012). α-Amylase inhibitors: a review of raw material and isolated compounds from plant source. *Journal of Pharmacy and Pharmaceutical Sciences*, *15*(1), 141-183. https://doi.org/10.18433/J35S3K

Sami, W., Ansari, T., Butt, N. S., & Ab Hamid, M. R. (2017). Effect of diet on type 2 diabetes mellitus: A review. *International Journal of Health Sciences*, *11*(2), 65-71.

Santos-Sánchez, N. F., Salas-Coronado, R., Villanueva-Cañongo, C., & Hernández-Carlos, B. (2019). Antioxidant compounds and their antioxidant mechanism. In *Antioxidants*. IntechOpen.

Sanyal, D. (2013). Diabetes is predominantly an intestinal disease. *Indian Journal of Endocrinology and Metabolism*, *17*(Suppl1), S64-S67. https://dx.doi.org/10.4103%2F2230-8210.119508

Saponaro, C., Gaggini, M., Carli, F., & Gastaldelli, A. (2015). The subtle balance between lipolysis and lipogenesis: a critical point in metabolic homeostasis. *Nutrients*, *7*(11), 9453-9474. https://doi.org/10.3390/nu7115475

Saravana, P. S., Tilahun, A., Gerenew, C., Tri, V. D., Kim, N. H., Kim, G. D.,& Chun, B.S. (2018). Subcritical water extraction of fucoidan from Saccharina japonica: optimization, characterization and biological studies. *Journal of Applied Phycology*, *30*(1), 579-590. https://doi.org/10.1007/s10811-017-1245-9

Sarian, M. N., Ahmed, Q. U., So'ad, M., Zaiton, S., Alhassan, A. M., Murugesu, S., & Latip, J. (2017). Antioxidant and antidiabetic effects of flavonoids: A structure-activity relationship based study. *BioMed Research International*, *2017*. https://doi.org/10.1155/2017/8386065

Sarker, M., Barua, M., Guerra, F., Saha, A., Aftab, A., Latif, A. M., & Islam, A. (2016). Double trouble: prevalence and factors associated with tuberculosis and diabetes comorbidity in Bangladesh. *PloS one*, *11*(10), e0165396.

Sears, B., & Perry, M. (2015). The role of fatty acids in insulin resistance. *Lipids in Health and Disease*, *14*(1), 121. https://doi.org/10.1186/s12944-015-0123-1

Seino, Y., & Yabe, D. (2013). Glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1: incretin actions beyond the pancreas. *Journal of Diabetes Investigation*, *4*(2), 108-130. https://doi.org/10.1111/jdi.12065

Semaan, D. G., Igoli, J. O., Young, L., Marrero, E., Gray, A. I., & Rowan, E. G. (2017). C. (2018). Action of phytochemicals on insulin signaling pathways accelerating glucose transporter (GLUT4) protein translocation. *Molecules*, *23*(2), 258. https://doi.org/10.3390/molecules23020258

Setyorini, D., Aanisah, R., Machmudah, S., Winardi, S., Kanda, H., & Goto, M..(2018). Extraction of Phytochemical Compounds from Eucheuma cottonii and Gracilaria sp using Supercritical CO2 Followed by Subcritical Water. *MATEC Web of Conferences*, *156*. https://doi.org/10.1051/matecconf/201815603051

Shabana, K., Okamoto, N., Sugita, Y., Shindo, K., Murata, T., Tamai, H., & Fujiwara, K. (2018). The findings of musculoskeletal ultrasonography on primary Sjögren's syndrome patients in childhood with articular manifestations and the impact of anti-cyclic citrullinated peptide antibody. *Modern Rheumatology*, *29*(5), 821-828. https://doi.org/10.1080/14397595.2018.1530849

Shah, V. N., Carpenter, R. D., Ferguson, V. L., & Schwartz, A. V. (2018). Bone health in type 1 diabetes. *Current Opinion in Endocrinology, Diabetes and Obesity*, *25*(4), 231-236.

Shahidi, F., Ambigaipalan, P. Phenolics and polyphenolics in foods, beverages and spices: Antioxidant activity and health effect. *Journal of Functional Foods*, *18*, 820–897. https://doi.org/10.1016/j.jff.2015.06.018

Sharma, A., Tate, M., Mathew, G., Vince, J. E., Ritchie, R. H., & De Haan, J. B. (2018). Oxidative stress and NLRP3-inflammasome activity as significant drivers of diabetic cardiovascular complications: therapeutic implications. *Frontiers in Physiology*, *9*, 114. https://doi.org/10.3389/fphys.2018.00114

Shitu, A., Izhar, S., & Tahir, T. M. (2015). Sub-critical water as a green solvent for production of valuable materials from agricultural waste biomass: a review of recent work. *Global Journal of Environmental Science and Management*, *1*(3), 255-264.

Siddiqui, A. A., Siddiqui, S. A., Ahmad, S., Siddiqui, S., Ahsan, I., & Sahu, K. (2013). Diabetes: Mechanism, pathophysiology and management-A review. *International Journal Drug Resources*, *5*(2), 1-23.

Silva Júnior, W. S. D., Godoy-Matos, A. F. D., & Kraemer-Aguiar, L. G. (2015). Dipeptidyl peptidase 4: a new link between diabetes mellitus and atherosclerosis. *BioMed Research International*, *2015*. https://doi.org/10.1155/2015/816164

Sinaga, M., Ganesan, K., Nair, S. K. P., & Gani, S. B. (2016). Preliminary phytochemical analysis and in vitro antibacterial activity of bark and seeds of Ethiopian neem (Azadirachta indica A. Juss). *World Journal of Pharmacy and Pharmaceutical Sciences*, *5*(4), 1714-1723.

Singh, J. P., Kaur, A., Shevkani, K., & Singh, N. (2016). Composition, bioactive compounds and antioxidant activity of common Indian fruits and vegetables. *Journal of Food Science and Technology*, *53*(11), 4056-4066.

Sivitz WI and Yorek MA (2010) Mitochondrial dysfunction in diabetes: from molecular mechanisms to functional significance and therapeutic opportunities. *Antioxidant Redox Signal***,** 537– 577.

Smith, U., & Kahn, B. B. (2016). Adipose tissue regulates insulin sensitivity: role of adipogenesis, de novo lipogenesis and novel lipids. *Journal of Internal Medicine*, *280*(5), 465-475.

Smith-Morris, C., Bresnick, G. H., Cuadros, J., Bouskill, K. E., & Pedersen, E. R. (2018). Diabetic retinopathy and the cascade into vision loss. *Medical Anthropology*, 1-14.

Smushkin, G., & Vella, A. (2010). What is type 2 diabetes. *Medicine*, *38*(11), 597-601.

Sola, D., Rossi, L., Schianca, G. P. C., Maffioli, P., Bigliocca, M., Mella, R., & Derosa, G. (2015). Sulfonylureas and their use in clinical practice. *Archives of Medical Science: AMS*, *11*(4), 840-848.

Solis-Herrera, C., Triplitt, C., Reasner, C., DeFronzo, R. A., & Cersosimo, E. (2018). Classification of diabetes mellitus. *Endotext.* https://www.ncbi.nlm.nih.gov/books/NBK279119

Song, R., Ismail, M., Baroutian, S., & Farid, M. (2018). Effect of Subcritical Water on Sui, X., Zhang, Y., & Zhou, W. (2016). In vitro and in silico studies of the inhibition activity of anthocyanins against porcine pancreatic α-amylase. *Journal of Functional Foods*, *21*, 50-57.

Stanford K. I., Middelbeek R. J. W., Goodyear L. J. (2015). Exercise effects on white adipose tissue: beiging and metabolic adaptations. *Diabetes*, *64*(6), 202-214. https://doi.org/10.2337/db14-0704

Sulaiman, I. S. C., Basri, M., Masoumi, H. R. F., Chee, W. J., Ashari, S. E., & Ismail, M. (2017). Effects of temperature, time, and solvent ratio on the extraction of phenolic compounds and the anti-radical activity of Clinacanthus nutans Lindau leaves by response surface methodology. *Chemistry Central Journal*, *11*(1), 54. https://doi.org/10.1186/s13065-017-0285-1

Świderska, E., Strycharz, J., Wróblewski, A., Szemraj, J., Drzewoski, J., & Śliwińska, A. (2018). Role of PI3K/AKT Pathway in Insulin-Mediated Glucose Uptake. In *Glucose Transport*. IntechOpen.

Tangvarasittichai, S. (2015). Oxidative stress, insulin resistance, dyslipidemia and type 2 diabetes mellitus. *World Journal of Diabetes*, *6*(3), 456-480. https://dx.doi.org/10.4239%2Fwjd.v6.i3.456

Taylor, R. (2012). Insulin resistance and type 2 diabetes. *Diabetes*, *61*(4), 778-779.

Telagari, M., & Hullatti, K. (2015). In-vitro α-amylase and α-glucosidase inhibitory activity of Adiantum caudatum Linn. and Celosia argentea Linn. extracts and fractions. *Indian Journal of Pharmacology*, *47*(4), 425-429. https://dx.doi.org/10.4103%2F0253-7613.161270

Telapolu, S., Kalachavedu, M., Punnoose, A. M., & Bilikere, D. (2018). MD-1, a poly herbal formulation indicated in diabetes mellitus ameliorates glucose uptake and inhibits adipogenesis–an in vitro study. *BMC Complementary and Alternative Medicine*, *18*(1), 113. https://doi.org/10.1186/s12906-018-2177-x

Thangavel, N., Al Bratty, M., Akhtar Javed, S., Ahsan, W., & Alhazmi, H. A. (2017). Targeting peroxisome proliferator-activated receptors using thiazolidinediones: Strategy for design of novel antidiabetic drugs. *International Journal of Medicinal Chemistry*, *2017*.

Thrasher, J. (2017). Pharmacologic management of type 2 diabetes mellitus: available therapies. *The American Journal of Cardiology*, *120*(1), 4-16.

Timar, B., Timar, R., Gaiță, L., Oancea, C., Levai, C., & Lungeanu, D. (2016). The impact of diabetic neuropathy on balance and on the risk of falls in patients with type 2 diabetes mellitus: a cross-sectional study. *PLoS One*, *11*(4), e0154654.

Tiwari, B. K., Abidi, A. B., Rizvi, S. I., & Pandey, K. B. (2018). Effect of oral supplementation of composite leaf extract of medicinal plants on biomarkers of oxidative stress in induced diabetic Wistar rats. *Archives of Physiology and Biochemistry*, *124*(4), 361-366.

Tran, L., Zielinski, A., Roach, A. H., Jende, J. A., Householder, A. M., Cole, E. E.,& Thompson, E. E. (2015). Pharmacologic treatment of type 2 diabetes: oral medications. *Annals of Pharmacotherapy*, *49*(5), 540-556.

Tungmunnithum, D., Thongboonyou, A., Pholboon, A., & Yangsabai, A. (2018). Flavonoids and other phenolic compounds from medicinal plants for pharmaceutical and medical aspects: An overview. *Medicines*, *5*(3), 93. https://doi.org/10.3390/medicines5030093

Ugwoke, C. K., Slokar, U., Nakayama, A., & Umek, N. (2017). Sulfonylureas in type 2 diabetes mellitus: current evidence, conflicts and clinical implications. *Nigerian Journal of Medicine*, *26*(1), 68-75.

Ullah, F., Ayaz, M., Sadiq, A., Hussain, A., Ahmad, S., Imran, M., & Zeb, A. (2016). Phenolic, flavonoid contents, anticholinesterase and antioxidant evaluation of Iris germanica var; florentina. *Natural product research*, *30*(12), 1440-1444.

Verboven, M., Van Ryckeghem, L., Belkhouribchia, J., Dendale, P., Eijnde, B. O., Hansen, D., & Bito, V. (2019). Effect of exercise intervention on cardiac function in type 2 diabetes mellitus: a systematic review. *Sports Medicine*, *49*(2), 255-268.

Vinayagam, R., Jayachandran, M., & Xu, B. (2016). Antidiabetic effects of simple phenolic acids: a comprehensive review. *Phytotherapy research*, *30*(2), 184-199.

Viollet, B., & Andreelli, F. (2011). AMP-activated protein kinase and metabolic control. *Diabetes-Perspectives in Drug Therapy*, *203*, 303-330.

Vo, T. H. N., Tran, N., Nguyen, D., & Le, L. (2016). An in silico study on antidiabetic activity of bioactive compounds in Euphorbia thymifolia Linn. *SpringerPlus*, *5*(1), 1359. https://doi.org/10.1186/s40064-016-2631-5

Wada, T., Churei, H., Takayanagi, H., Iwasaki, N., Ueno, T., Takahashi, H., & Uo, M. (2018). Improvement of the Shock Absorption Ability of a Face Guard by Incorporating a Glass-Fiber-Reinforced Thermoplastic and Buffering Space. *BioMed research international*, *2018*.

Wang, F., Zhang, Y., Yu, T., He, J., Cui, J., Wang, J., & Fan, J. (2018). Oat globulin peptides regulate antidiabetic drug targets and glucose transporters in Caco-2 cells. *Journal of Functional Foods*, *42*, 12-20. https://doi.org/10.1016/j.jff.2017.12.061

Wang, Feilong, Song Zhang, Ivan Vuckovic, Ryounghoon Jeon, Amir Lerman, Clifford D. Folmes, Petras P. Dzeja, and Joerg Herrmann. "Glycolytic stimulation is not a requirement for M2 macrophage differentiation." *Cell Metabolism*, 28 (3), 463-475.

Watcharachaisoponsiri, T., Sornchan, P., Charoenkiatkul, S., & Suttisansanee, U. (2016). The α-glucosidase and α-amylase inhibitory activity from different chili pepper extracts. *International Food Research Journal*, *23*(4), 1439-1445.

Wu, Y., Ding, Y., Tanaka, Y., & Zhang, W. (2014). Risk factors contributing to type 2 diabetes and recent advances in the treatment and prevention. *International Journal of Medical Sciences*, *11*(11), 1185-1200. https://dx.doi.org/10.7150%2Fijms.10001

Xiao, J., Kai, G., Ni, X., Yang, F., & Chen, X. (2011). Interaction of natural polyphenols with α-amylase in vitro: molecular property–affinity relationship aspect. *Molecular BioSystems*, *7*(6), 1883-1890.

Xu, D. P., Li, Y., Meng, X., Zhou, T., Zhou, Y., Zheng, J. & Li, H. B. (2017). Natural antioxidants in foods and medicinal plants: Extraction, assessment and resources. *International Journal of Molecular Sciences*, *18*(1), 96. https://doi.org/10.3390/ijms18010096

Xu, H., Wang, W., Liu, X., Yuan, F., & Gao, Y. (2015). Antioxidative phenolics obtained from spent coffee grounds (Coffea arabica L.) by subcritical water extraction. *Industrial Crops and Products*, *76*, 946-954. https://doi.org/10.1016/j.indcrop.2015.07.054

Yadav, A., Kumari, R., Yadav, A., Mishra, J. P., Srivatva, S., & Prabha, S. (2016). Antioxidants and its functions in human body-A Review. *Research in Environment and Life Science*, *9*(11), 1328-1331.

Yahaya, E. S., Cordier, W., Steenkamp, P. A., & Steenkamp, V. (2018). Effect of ethnomedicinal extracts used for wound healing on cellular migration and intracellular reactive oxygen species release in SC-1 fibroblasts. *South African Journal of Botany*, *118*, 11-17. https://doi.org/10.1016/j.sajb.2018.06.003

Yan, J., Zhang, G., Pan, J. and Wang, Y. (2014). α-glucosidase inhibition by luteolin: Kinetics, interaction and molecular docking. *International Journal of Biological Macromolecules*, *64*, 213-223.

Yang, L., Qu, H., Mao, G., Zhao, T., Li, F., Zhu, B., & Wu, X. (2013). Optimization of subcritical water extraction of polysaccharides from Grifola frondosa using response surface methodology. *Pharmacognosy Magazine*, *9*(34), 120-129. https://dx.doi.org/10.4103%2F0973-1296.111262

Yang, X., Yang, J., Xu, C., Huang, M., Zhou, Q., Lv, J., & Zhao, P. (2015). Antidiabetic effects of flavonoids from Sophora flavescens EtOAc extract in type 2 diabetic KK-ay mice. *Journal of Ethnopharmacology*, *171*, 161-170. https://doi.org/10.1016/j.jep.2015.05.043

Ye, J. (2013). Mechanisms of insulin resistance in obesity. *Frontiers of Medicine*, *7*(1), 14-24.

Yoshida, H.; Izhar, S.; Nishio, E.; Utsumi, Y.; Kakimori, N.; Asghari Feridoun, S., (2014). Recovery of indium from TFT and CF glasses in LCD panel wastes using sub-critical water, *Solar Energy Mater. Solar Cells*, *125*, 14–19. https://doi.org/10.1016/j.solmat.2014.02.009

Yusro, F., Ohtani, K., & Kubota, S. (2016). Inhibition of α-Glucosidase by Methanol Extracts from Wood Bark of Anacardiaceae, Fabaceae, Malvaceae and Phyllanthaceae Plants Family in West Kalimantan, Indonesia, *Kuroshio Science*,*9*(2)108-122.

Yusuf, M. I., Susanty, S., & Fawwaz, M. (2018). Antioxidant and Antidiabetic Potential of Galing Stem Extract (Cayratia trifolia Domin). *Pharmacognosy Journal*, *10*(4), 686-690.

Zhang,Z ., Baroutian, S., Munir, M,T., Young, B,R. (2017). Variation in metals during wet oxidation of sewage sludge. *Bioresources and Technology*, *245*, 234-241. https://doi.org/10.1016/j.biortech.2017.08.164

Zhao, L., Ma, K., & Yang, Z. (2015). Changes of water hydrogen bond network with different externalities. *International Journal of Molecular Sciences*, *16*(4), 8454-8489. https://doi.org/10.3390/ijms16048454

Zheng, T., Gao, Y., Baskota, A., Chen, T., Ran, X., & Tian, H. (2014). Increased plasma DPP4 activity is predictive of prediabetes and type 2 diabetes onset in chinese over a four-year period: result from the China National Diabetes and Metabolic Disorders Study. *The Journal of Clinical Endocrinology & Metabolism*, *99*(11), 2330-2334. https://doi.org/10.1210/jc.2014-1480

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LIST OF PUBLICATIONS

Journal

Zabidi, N.A, Ishak, N. A., Hamid, M., Ashari, S.E (2019). Subcritical water extraction of antioxidants from *Curculigo latifolia* root. *Journal of Chemistry*.

Ishak, N.A & Zabidi, N. A. (2019). Hypoglycemic Activity of *Curculigo latifolia* on insulin and Glucose Uptake Activities in in vitro. *Journal of Engineering and Applied Sciences*, 14, 7502-7508.

Ishak, N. A., Rashid, M. Y. A., & Zabidi, N. A. (2019). Antidiabetic and Antioxidant Capacities of Local Banana Peels Extract by Using Subcritical Water Extraction Technique. *Ulum Islamiyyah*, *26*, 19-30.

Conference / Proceedings

Zabidi, N.A & Ishak, N. A (2018). Total Phenolic Content, Antioxidant Activity of *Curculigo Latifolia* Extract by Subcritical Water Extraction. Poster session presented at the International Conference on Natural Products, 19-21 March 2018, Penang, Malaysia (Poster).

Zabidi, N.A & Ishak, N. A (2019). Antidiabetic potential of *Curculigo latifolia* root extract through inhibition of α-amylase and α-glucosidase via molecular docking studies. Poster session presented at the International Food Research Conference (IFRC), 27-29 August 2019, Putrajaya, Selangor, Malaysia (Poster).

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