STUDY ON ANTIOXIDANT AND ANTIDIABETIC PROPERTIES OF PHLOROGLUCINOL FROM BROWN MACROALGAE *Padina australis* Hauck

AMARCHAND CHORDIA MURUGAN

Doctor of Philosophy

(BIOTECHNOLOGY)

UNIVERSITI MALAYSIA PAHANG

SUPERVISOR'S DECLARATION

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

_____

(Supervisor's Signature)

Full Name : DR. NATANAMURUGARAJ GOVINDAN

Position : SENIOR LECTURER

Date :

_____

(Co-supervisor's Signature)

Full Name : PROF. DATO' DR. MASHITAH BINTI MOHD YUSOFF

Position : PROFESSOR

Date :

STUDENT'S DECLARATION

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

_____

(Student's Signature)

Full Name : AMARCHAND CHORDIA MURUGAN

ID Number : PKT12001

Date : 10 AUGUST 2018

STUDY ON ANTIOXIDANT AND ANTIDIABETIC PROPERTIES OF PHLOROGLUCINOL FROM BROWN MACROALGAE *Padina australis* Hauck

AMARCHAND CHORDIA MURUGAN

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

Faculty of Industrial Sciences & Technology

UNIVERSITI MALAYSIA PAHANG

AUGUST 2018

ACKNOWLEDGEMENTS

This PhD thesis would not have been possible without the inspiration and support of a number of wonderful individuals, my thanks and appreciation to all of them for being part of this journey and making this thesis possible. I owe my deepest gratitude to my supervisors Dr. Natanamurugaraj Govindan and Assoc. Prof. Dr. Rezaul Karim. Without their enthusiasm, encouragement, support and continuous optimism this thesis would hardly have been completed. I express my warmest gratitude to my co-supervisor Prof. Dato' Dr. Mashitah Binti Mohd Yusoff for her constant encouragement and support during my study. Besides my advisors, I would like to thank the Assoc. Prof. Dr. Gaanty Pragas Maniam, for his encouragement, insightful comments, and valuable inputs during the whole study. His guidance into the world of pharmacology has been a valuable input for this thesis. I also want to express my gratitude to Prof. Dr. K. Masilamani, Head, Pharmacology Department, Jaya College of Pharmacy, Chennai, Tamil Nadu, India. He has made available his support in a number of ways, especially towards the completion of this thesis.

I am forever thankful to my colleagues at the Faculty of Industrial Sciences & Technology, Universiti Malaysia Pahang for their friendship and support, and for creating a cordial working environment. I thankfully acknowledge the contributions of Science Officers of FIST laboratory & Central laboratory, UMP for taking care of all the technical, administrative matters and making it possible to carry out this work in a conducive environment. I am particularly thankful to Institute of Postgraduate Studies and Faculty of Industrial Sciences & Technology for awarding me Doctoral Scheme Scholarship.

It is a pleasure to thank my friends at the International Students Hostel, UMP for the wonderful times we shared, specially the weekend hangouts. In addition, I would like to thank all my friends in Universiti Malaysia Pahang who gave me the necessary distractions from my research and made my stay in Malaysia memorable.

Finally, my deep and sincere gratitude to my family for their continuous and unparalleled love, help and support. I am grateful to my brother Ajaypraveen Chordia Murugan and my sisters Sophia Murugan and Ashwini Murugan for always being there for me as a friend. I am forever indebted to my parents Mr. Murugan Vellaiappan and Mrs. Paranjothi Murugan for giving me the opportunities and experiences that have made me who I am. They selflessly encouraged me to explore new directions in life and seek my own destiny. This journey would not have been possible if not for them, and I dedicate this milestone to them.

Dedicated to my parents

Mr. Murugan Vellaiappan & Mrs. Paranjothi Murugan

ABSTRAK

Pencirian antidiabetik dan potensi antioksidan ekstrak polifenol dari Padina australis, rumpai laut perang telah dikaji. Ekstrak metanol (80:20 MeOH:Air suling, v/v) dari P. australis dibahagikan kepada lima bahagian dengan pelarut berbeza dan fungsi menghalang enzim α-glucosidase dan enzim α-amilase, pengekstrakan aktiviti radikal terhadap 1,1-diphenyl-2-picrylhydrazyl (DPPH), kuasa antioksida pengurangan ferik (FRAP), aktiviti kelat ion ferus (FIC) dan sifat pemutihan beta karotena telah dinilai. Pemeriksaan pencegahan antiradikal dan antidiabetik adalah signifikan secara statistik kerana ekstrak yang berbeza dari P. australis menghalang enzim secara in vitro dan in vivo. Di antara lima pecahan yang tersebut, pecahan n-butanol menunjukkan aktiviti menghambat antiradikal dan antidiabetik yang lebih tinggi berbanding dengan lain. Ekstrak metanol tertumpu kepada analisis TLC dan HPLC untuk mengenal pasti molekul bioaktif yang terdapat di dalam campuran ekstrak. Analisis LC-MS mengenai pecahan kelima n-butanol menunjukkan kehadiran tiga sebatian Phlorotannin iaitu Phloroglucinol, Eckol, dan Phlorofucofuroeckol A. Teknik kromatografi digunakan untuk mengasingkan Phloroglucinol untuk kajian selanjutnya. Konstituen aktif telah diasingkan dan dibersihkan daripada pecahan aktif dan dikaji untuk kesan antidiabetik dalam tikus diabetic Streptozotocin. Antara pecahan yang diuji, pecahan n-butanol mempunyai aktiviti penghambatan α-glucosidase dan α-amilase yang signifikan dengan nilai IC50 2.06 ± 0.14 dan 2.90 ± 0.08 mg/mL berbanding dengan Acarbose. Ketoksikan akut sebatian tulen yang dipencilkan pada dos 20 dan 40 mg/kg dalam tikus Swiss Albino mempunyai aktiviti antidiabetik yang ketara dengan peningkatan glukosa, lipid dan parameter antioksidan. Kajian toksikologi juga menunjukkan bahawa sebatian tulen Phloroglucinol tidak mempunyai kesan toksik dalam organ dalaman; berdasarkan parameter biokimia dan haematologi. Penemuan ini menunjukkan bahawa penggunaan diet Padina australis dan sebatian terpencil boleh digunakan sebagai ubat untuk rawatan kencing manis. Hasil kajian ini boleh membantu untuk membangunkan agen antihiperglisemik oral baru dalam pengurusan penyakit kencing manis (diabetes mellitus).

ABSTRACT

Diabetes is a metabolic disorder characterized by high levels of blood glucose. It is caused by the pancreatic insufficiency or by insulin resistance. Marine macroalgae extracts have been established to have strong antidiabetic and antioxidant properties. In the present study, the antidiabetic and antioxidant potential of polyphenolic extract from a brown seaweed *Padina australis* was evaluated. Methanolic (80:20 % of MeOH: Deionized Water v/v) extract of *P. australis* was partitioned with five different solvents. The carbolytic enzyme inhibiting functions, radical scavenging activity assay against 2,2-diphenyl-1-picrylhydrazyl (DPPH), ferric reducing antioxidant power (FRAP), ferrous ion chelating (FIC) activity, beta-carotene bleaching properties are evaluated. The antiradical and antidiabetic inhibition assays were statistically significant as the different extracts of *P. australis* inhibited the enzymes in vitro and in vivo. Among the five different fractions, n-butanol fraction showed significantly higher antiradical and antidiabetic inhibitory activity. The methanolic extract was subjected to TLC and HPLC analysis to identify the bioactive molecules present in the mixture of extract. Further LC-MS analysis of n-butanol 5th fraction revealed the presence of three Phlorotannin compounds namely Phloroglucinol, Eckol, and Phlorofucofuroeckol A. Sephadex LH-20, column chromatography technique, was employed to isolate Phloroglucinol compound for further study. Phloroglucinol isolated and purified from the active fraction was evaluated for antidiabetic effect in Streptozotocin-induced diabetic rats. Among the tested portions, n-butanol fraction had significant α-glucosidase and α-amylase inhibitory activity with IC_{50} value 2.06 ± 0.14 and 2.90 ± 0.08 mg/mL respectively, as compared to Acarbose. Acute toxicity of the isolated pure compound at 20 and 40 mg/kg doses in Swiss Albino mice was found to have potent antidiabetic activity by ameliorating glucose, lipids, and antioxidant parameters. The toxicology studies also showed that the pure compound Phloroglucinol did not have any toxic effects in the internal organs; biochemical and hematological parameters. These findings suggest that the dietary use of *Padina australis* and the isolated compound Phloroglucinol can be used as medicine for the treatment of diabetes. This work could help to develop new oral antihyperglycemic agent in the management of diabetes mellitus.

TABLE OF CONTENT

DECLARATION

TITLE PAGE

ACKNOWLEDGEMENTS **ii**

ABSTRAK **iv**

ABSTRACT **v**

TABLE OF CONTENT **vi**

LIST OF TABLES **xii**

LIST OF FIGURES **xiii**

LIST OF SYMBOLS **xv**

LIST OF ABBREVIATIONS **xvi**

CHAPTER 1 INTRODUCTION **1**

1.1 Introduction 1

1.2 Background Statement 3

1.3 Problem statements 4

1.4 Research Objectives 4

1.5 Scope of research 5

1.6 Thesis layout 5

CHAPTER 2 LITERATURE REVIEW **6**

2.1 Introduction 6

2.2 Diabetes Mellitus 7

2.2.1 Mechanism of Glucose Homeostasis in Humans 8

2.2.2 Health benefits of Polyphenols 10

2.2.3 Role of polyphenols on metabolism of carbohydrates 10

2.3 Diabetes-Induced Oxidative stress and use of Antioxidants 12

2.3.1 Oxidative stress and Reactive Oxygen Species 12

2.3.2 Damages Caused by Reactive Oxygen Species in Human Body 13

2.3.3 Oxidative stress induced diabetes complications 14

2.3.4 Antioxidants defense mechanism against oxidative stress 14

2.3.5 Epidemiological Evidence and Experimental Models 15

2.4 Prevalence of Diabetes Mellitus in Malaysia 16

2.4.1 Drug Treatment Available for Diabetes in Malaysia 18

2.5 Macroalgae-Derived Phlorotannins 18

2.5.1 Macroalgae Carbolytic Enzyme Inhibitory Activity 20

2.6 *In Vivo* Animal Model Study for Antidiabetic Effects 21

2.6.1 Pharmacological Induction of Diabetes Mellitus 22

2.6.2 Chemical Induction of Diabetes Mellitus in Animal Models 22

2.6.3 Streptozotocin-Induced model of Diabetes Mellitus 23

2.7 Summary 24

CHAPTER 3 METHODOLOGY 25

3.1 Introduction 25

3.2 Chemicals and Glassware 25

3.3 Sample Collection 25

3.3.1 Sample Identification 27

3.3.2 Preparation of Sample 28

3.4 Extraction of Phlorotannins 28

3.5 Determination of Phenolic Content and Antioxidant Properties 28

3.5.1 Total Phenolic Content (TPC) 28
3.5.2 2,2-diphenyl-1-picrylhydrazyl (DPPH) Radical Scavenging Activity 29
3.5.3 Ferric- Reducing Antioxidant Power (FRAP) 29
3.5.4 Ferrous Ion Chelating (FIC) Assay 30
3.5.5 Beta Carotene Bleaching (BCB) Assay 30
3.6 Enzyme Inhibition Study 31
3.6.1 In vitro α-Glucosidase Inhibition Assay 31
3.6.2 In vitro α-Amylase Inhibition Assay 31
3.7 Isolation and Purification 32
3.7.1 Column Chromatography 32
3.7.2 Thin Layer Chromatography Analysis 32
3.7.3 High-Performance Liquid Chromatography Analysis 32
3.8 Structure Elucidation 33
3.8.1 LC-MS Profiling 33
3.8.2 Mass Spectrometry Analysis 33
3.9 Antidiabetic Experimental Animals 33
3.9.1 Acute Toxicity Study 34
3.9.2 Streptozotocin-Induced Diabetic Rats 34
3.10 Estimation Blood and Biochemical Parameters 35
3.10.1 Estimation of Glucose 35
3.11 Estimation Protein Profile 35
3.11.1 Total Proteins 35
3.11.2 Total Albumins 36
3.11.3 Estimation of Globulins 36
3.12 Plasma Lipid Profile (Cholesterol, Triglyceride, HDL, LDL, and VLDL) 36

3.12.1 Estimation of Cholesterol 36
3.12.2 Estimation of Triglycerides 36
3.12.3 HDL-Cholesterol 37
3.12.4 LDL-Cholesterol 37
3.13 Plasma Enzymes Profile (AST, ALT, ALP, AP LDH and CPK) 37
3.13.1 Assay of Aspartate Transaminase (AST) 38
3.13.2 Assay of Alanine Transaminase (ALT) 38
3.13.3 Assay of Alkaline Phosphatase (ALP) 38
3.13.4 Assay of Acid Phosphatase (AP) 38
3.13.5 Lactate Dehydrogenase (LD) 38
3.13.6 Creatinine Phosphatase (CPK) 39
3.14 Estimation of Antioxidant Profile 39
3.14.1 Assay of Superoxide Dismutase 39
3.14.2 Assay of Catalase 39
3.14.3 Assay of Glutathione Peroxidase 40
3.14.4 Estimation of Reduced Glutathione 40
3.14.5 Estimation of Lipid Peroxidation 40
3.15 Animal Toxicological Studies 41
3.15.1 Experimental Animals 41
3.15.2 Laboratory Investigations 41
3.15.3 Hematological Investigations 41
3.15.4 Biochemical Investigations 41
3.15.5 Necropsy 42
3.15.6 Histopathology 42
3.16 Statistical Analysis 42

CHAPTER 4 RESULTS AND DISCUSSION **43**

4.1 Introduction 43

4.2 Sample Collection 43

4.3 Extraction Yield 44

4.3.1 Total Phenolic Content 45

4.3.2 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radical scavenging activity 46

4.3.3 Ferric reducing antioxidant power (FRAP) 48

4.3.4 Ferrous ion chelating (FIC) assay 49

4.3.5 Beta-carotene bleaching (BCB) assay 50

4.3.6 Pearson's Correlation analysis between the total phenolic content and antioxidant capacity 51

4.3.7 α -Glucosidase and α-Amylase Inhibitory Activity 52

4.4 Purification of Crude Extract 54

4.4.1 Sephadex LH-20 Column Chromatography 55

4.4.2 Yield Percentage 55

4.4.3 Total Phenolic content 56

4.4.4 DPPH Scavenging Activity of Purified n-Butanol Fraction 56

4.4.5 α-Glucosidase and α-Amylase Inhibitory Activity 57

4.5 Structural Characterization of Purified Extract 58

4.5.1 HPLC profiling 58

4.5.2 LC-MS profile 59

4.5.3 TLC Separation of n-Butanol Fraction 62

4.5.4 NMR characterization 63

4.6 Animal Model Study for Antihyperglycemic Effect of Phloroglucinol 67

4.6.1 Acute toxicity 67

4.6.2 Effect of Phloroglucinol on Serum Glucose Level 67

4.6.3 Effect of Phloroglucinol on Serum Protein Levels 70

4.6.4 Effect of Phloroglucinol on Serum Lipid levels 71

4.6.5 Effect of Phloroglucinol on Plasma Enzyme profiles 74

4.6.6 Effect of Phloroglucinol on Antioxidant Enzyme profile 77

4.7 Animal Toxicology Studies of Phloroglucinol 80

4.7.1 Organ weight 80

4.7.2 Haematology Investigation of Phloroglucinol Toxicity 82

4.7.3 Biochemical Parameters evaluation of Phloroglucinol Toxicity 84

4.7.4 Histopathological Examination 86

4.8 Summary 90

CHAPTER 5 CONCLUSION **91**

5.1 Introduction 91

5.2 Conclusion 91

5.3 Recommendations 91

REFERENCES **93**

APPENDIX A LC-MS PROFILING **110**

APPENDIX B ETHICAL CLEARANCE CERTIFICATE **113**

APPENDIX C LIST OF PUBLICATIONS **115**

LIST OF TABLES

Table 2.1	Overview of bioactive phlorotannins (polyphenols) isolated from brown marine algae.	19
Table 4.1	Effect of different solvent extraction on the yield percentage of Padina australis Hauck	45
Table 4.2	DPPH IC50 free radical scavenging activity of P. australis crude extracts from different solvents	48
Table 4.3	Pearson's correlation coefficient value between Total Phenolics and antioxidant potential of different solvent crude extracts of Padina australis Hauck.	52
Table 4.4	α-Glucosidase inhibition activity of different solvent crude fractions of Padina australis Hauck.	53
Table 4.5	α-Amylase inhibition activity of different solvent crude fractions of Padina australis Hauck.	54
Table 4.6	Yield percentage of n-butanol fraction subjected to Sephadex LH-20 column chromatography.	55
Table 4.7	Total phenolic content of purified butanol fractions of P. australis.	56
Table 4.8	DPPH Antioxidant activity of purified n-butanol fractions of P.australis.	57
Table 4.9	Carbolytic enzyme inhibitiory activity of purified butanol fractions of Padina australis Hauck.	58
Table 4.10	Effect of Phloroglucinol on Serum glucose level in Streptozotocin induced diabetic rats.	69
Table 4.11	Effect of Phloroglucinol on the Serum protein level in Streptozotocin induced diabetic rats.	70
Table 4.12	Effect of Phloroglucinol on the Total Lipid profile in Streptozotocin induced diabetic rats.	73
Table 4.13	Effect of Phloroglucinol on the Plasma Enzyme profile in Streptozotocin induced diabetic rats.	76
Table 4.14	Effect of Phloroglucinol on the Antioxidant enzyme profile in Streptozotocin induced diabetic rats.	79
Table 4.15	Organ weight of Streptozocin-induced diabetic and Phloroglucinol treated mice.	81
Table 4.16	Hematological parameters of rats in sub-acute toxicity of Phloroglucinol on 60th day.	83
Table 4.17	Biochemical parameters of rats in sub acute toxicity of Phloroglucinol on 60th day.	85

LIST OF FIGURES

Figure 2.1	Mechanism of glucose homeostasis	9
Figure 2.2	Generation of reactive species in humans under hyperglycemic condition.	13
Figure 3.1	Location map for sample collection, Pantai Penyabong, Mersing, Johor, Malaysia	26
Figure 3.2	Collection of seaweeds from Pantai Penyabong	27
Figure 4.1	Specimen picture of Padina australis Hauck collected from rocky shores of Pantai Penyabong, Johor, Malaysia	44
Figure 4.2	Total phenolic content of different polarity solvent extracts of Padina australis Hauck (mg GAE/g).	46
Figure 4.3	DPPH free radical scavenging ability of different solvent crude extracts of P. australis	47
Figure 4.4	Ferric reducing antioxidant power (FRAP) of different solvent crude extract of P. australis	49
Figure 4.5	Ferrous ion chelating ability of different solvent crude extract of P. australis	50
Figure 4.6	Antioxidant activity of different solvent extracts of P. australis as determined by β-carotene bleaching assay	51
Figure 4.7	HPLC-DAD chromatogram of crude n-butanol extract at 254nm.	59
Figure 4.8	HPLC-DAD chromatogram of n-butanol 5th fraction at 254nm.	59
Figure 4.9	2D chemical structure of Phloroglucinol molecule isolated from P. australis	60
Figure 4.10	2D Chemical structure of Eckol molecule isolated from P. australis	61
Figure 4.11	2D Chemical structure of Phlorofucofuroeckol-A molecule isolated from P. australis	61
Figure 4.12	Thin layer chromatography separation of n-butanol 5th fraction.	62
Figure 4.13	H1 NMR profile of isolated Phloroglucinol from P. australis n-butanol 5th fraction.	64
Figure 4.14	C13 NMR profile of isolated Phloroglucinol from P. australis from n-butanol 5th fraction.	65
Figure 4.15	CDEPT NMR profile of isolated Phloroglucinol from P. australis from n-butanol fraction.	66
Figure 4.16	L.S. of Liver	87
Figure 4.17	L.S. of Kidney	87
Figure 4.18	L.S. of Brain	88
Figure 4.19	L.S. of Heart	88
Figure 4.20	L.S. of Lungs.	89

Figure 4.21 L.S. of Spleen 89

LIST OF SYMBOLS

℃	Degree Celsius
µg	microgram
µL	microliter
α	alpha
β	beta
γ	gamma
%	percentage

LIST OF ABBREVIATIONS

ACC	Acetyl-CoA carboxylase
ACE	Angiotensin Converting Enzyme
AChE	Acetylcholine Esterase
AGE	Advanced Glycation Products
Akt	Protein Kinase B (PKB)
ALP	Alkaline Phosphatase
ALS	Alloxan Sensitive
ALT	Alanine Transaminase
ALX	Alloxan
AMPK	AMP-Activated Protein Kinase
ANOVA	Analysis of Variance
AOA	Antioxidant Activity
AP	Acid Phosphatase
AST	Aspartate Transaminase
AUC	Area Under Cover
BAM	Biologically Active Metabolite
BCB	Beta Carotene Bleaching
BChE	Butylcholine Esterase
BUN	Blood Urea Nitrogen
BuOH	Butanol
BW	Body Weight
CAT	Catalase
CPK	Creatinine Phosphatase
DHA	Docosahexaenoic Acid
DM	Diabetes Mellitus

DMSO	Dimethyl Sulfoxide
DNA	Deoxyribo Nucleic Acid
DNS	Dinitro Salicylic Acid
DPHC	Diphlorethohydroxycarmalol
DPPH	2,2-diphenyl-1-picrylhydrazyl
DR	Degradation Rate
EDTA	Ethylene Diamine Tetraacetic Acid
EPA	Eicosapentaenoic Acid
ERK 1/2	Extracellular Signal-Regulated Protein Kinases 1 & 2
ESR	Electron Spin Resonance Spectroscopy
EtOAc	Ethyl Acetate
FIC	Ferrous Ion Chelating
FRAP	Ferric- Reducing Antioxidant Power
G6Pase	Glucose - 6- Phosphatase
GAE	Gallic Acid Equivalent
GDIP	Glucose-Dependent Insulinotropic Polypeptide
GIP	Gastric Inhibitory Polypeptide
GK	Goto-Kakizaki
GLP-1	Glucagon-Like Polypheptide-1
GLUT	Glucose Transporter
GSH-px	Glutathione Peroxidase
GTG	Gold Thioglucose
Hb	Haemoglobin
HCT	Hematocrit
HDL	High Density Lipid
HGK	Hepatic Glucokinase

HPLC	High Performance Liquid Chromatography
HUVECs	Human Umbilical Vein Endothelial Cells
IRS	Insulin Receptor Substrate
kDa	kilo Dalton
KK	Kuo Kondo
KK/A_y	yellow KK obese
L.S.	Longitudinal Section
LC-MS	Liquid Chromatography Coupled Mass Spectrometry
LD	Lactate Dehydrogenase
LDL	Low Density Lipid
MALDI	Matrix Assisted Laser Desorption/Ionization
MeOH	Methanol
MS	Mass Spectrometry
MVC	Mean Corpuscular Volume
NO	Nitrous Oxide
NZO	New Zealand Obese
OD	Optical Density
OLETF	Otuska Long Evans Tokushima Fatty
PBS	Phosphate Buffer Saline
PEPCK	Phosphoenolpyruvate Carboxykinase
PI3K	Phosphatidylinositide 3-Kinases
PKA	cAMP-Dependent Protein Kinase
PLT	Platelets
p-NPG	p-nitrophenyl α-D- glucopyranoside
PPAR	Peroxisome Proliferator Activated Receptor
ppm	Part Per Million

PTP	Phosphotyrosine Phosphatase
RBC	Red Blood Cell
RIA	Radioimmuno Assay
RLAR	Rat Lens Aldolase Reductase
ROS	Reactive Oxygen Species
SD	Standard Deviation
SE	Standard Error
SGLT	Sodium Glucose Co-Transporters
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SHR/N-cp	Spontaneously Hypertensive rat/NIH-corpulent;
SOD	Super Oxide Dismutase
STZ	Streptozotocin
T.S.	Transverse Section
TBARS	Thiobarbituric Acid Reactive Substances
TLC	Thin Layer Chromatography
TOF	Time of Flight
TPC	Total Phenolic Content
TSOD	Tsumara Suzuki Obese Diabetes
UPLC	Ultra Performance Liquid Chromatography
VLDL	Very Low Density Lipoprotein
VMH	Ventromedial Hypothalamus
WBC	White Blood Cell
WHO	World Health Organisation
ZDF	Zucker Diabetic Fatty

"Nothing in life is to be feared, it is only to be understood. Now is the time to understand more, so that we may fear less." - Marie Curie

REFERENCES

Adeneye, A., Ajagbonna, O., Adeleke, T. and Bello, S. (2006). Preliminary toxicity and phytochemical studies of the stem bark aqueous extract of Musanga cecropioides in rats. *Journal of Ethnopharmacology, 105*(3), 374-379.

Aggarwal, B. B. and Shishodia, S. (2006). Molecular targets of dietary agents for prevention and therapy of cancer. *Biochemical Pharmacology, 71*(10), 1397-1421.

Ahmad, M. F., Ashraf, S. A., Ahmad, F. A., Ansari, J. A. and Siddiquee, M. R. A. (2011). Nutraceutical market and its regulation. *American Journal of Food Technology, 6*(5), 342-347.

American Diabetes, A. (2016). Standards of Medical Care in Diabetes-2016 Abridged for Primary Care Providers. *Clinical Diabetes : A Publication of the American Diabetes Association, 34*(1), 3-21.

Apel, K. and Hirt, H. (2004). Reactive Oxygen Species: Metabolism, Oxidative Stress, and Signal Transduction. *Annual Review of Plant Biology, 55*(1), 373-399.

Apostolidis, E. and Lee, C. (2010). In Vitro potential of ascophyllum nodosum phenolic antioxidant-mediated α-glucosidase and α-amylase inhibition. *Journal of Food Science, 75*(3).

Arnold, T. M. and Targett, N. M. (2002). Marine tannins: the importance of a mechanistic framework for predicting ecological roles. *Journal of Chemical Ecology, 28*(10), 1919-1934.

Aronoff, S. L., Berkowitz, K., Shreiner, B. and Want, L. (2004). Glucose metabolism and regulation: beyond insulin and glucagon. *Diabetes Spectrum, 17*(3), 183-190.

Asgary, S., Rafieian-Kopaei, M., Shamsi, F., Najafi, S. and Sahebkar, A. (2014). Biochemical and histopathological study of the anti-hyperglycemic and anti-hyperlipidemic effects of cornelian cherry (Cornus mas L.) in alloxan-induced diabetic rats. *Journal of Complementary and Integrative Medicine,* 11, 63-70.

Asmat, U., Abad, K. and Ismail, K. (2016). Diabetes mellitus and oxidative stress-A concise review. *Saudi Pharmaceutical Journal, 24*(5), 547-553.

Athukorala, Y., Kim, K.-N. and Jeon, Y.-J. (2006). Antiproliferative and antioxidant properties of an enzymatic hydrolysate from brown alga, Ecklonia cava. *Food and Chemical Toxicology, 44*(7), 1065-1074.

Augusti, K. and Sheela, C. (1996). Antiperoxide effect of S-allyl cysteine sulfoxide, an insulin secretagogue, in diabetic rats. *Experientia, 52*(2), 115-119.

Ayeleso, A., Brooks, N., Oguntibeju, O. and Mukwevho, E. (2016). Natural antioxidant vitamins: A review of their beneficial roles in management of diabetes mellitus

and its complications. *Tropical Journal of Pharmaceutical Research, 15*(6), 1341-1348.

Bae, Y. S., Lee, J. H., Choi, S. H., Kim, S., Almazan, F., Witztum, J. L. and Miller, Y. I. (2009). Macrophages Generate Reactive Oxygen Species in Response to Minimally Oxidized Low-Density Lipoprotein. *Toll-Like Receptor 4– and Spleen Tyrosine Kinase–Dependent Activation of NADPH Oxidase 2, 104*(2), 210-218.

Balakumar, P., Maung-U, K. and Jagadeesh, G. (2016). Prevalence and prevention of cardiovascular disease and diabetes mellitus. *Pharmacological Research, 113*, 600-609.

Bansal, P., Paul, P., Mudgal, J., G. Nayak, P., Thomas Pannakal, S., Priyadarsini, K. I. and Unnikrishnan, M. K. (2012). Antidiabetic, antihyperlipidemic and antioxidant effects of the flavonoid rich fraction of Pilea microphylla (L.) in high fat diet/streptozotocin-induced diabetes in mice. *Experimental and Toxicologic Pathology, 64*(6), 651-658.

Barchan, A., Bakkali, M., Arakrak, A., Pagán, R., & Laglaoui, A. (2014). The effects of solvents polarity on the phenolic contents and antioxidant activity of three Mentha species extracts. *Int J Curr Microbiol App Sci*, *3*(11), 399-412.

Barzilai, N., Huffman, D. M., Muzumdar, R. H. and Bartke, A. (2012). The Critical Role of Metabolic Pathways in Aging. *Diabetes, 61*(6), 1315-1322.

Basu, A., Morris, S., Nguyen, A., Betts, N. M., Fu, D. and Lyons, T. J. (2016). Effects of Dietary Strawberry Supplementation on Antioxidant Biomarkers in Obese Adults with Above Optimal Serum Lipids. *Journal of Nutrition and Metabolism, 2016*, 9.

Berchtold, L. A., Prause, M., Størling, J. and Mandrup-Poulsen, T. (2016). Chapter Five - Cytokines and Pancreatic β-Cell Apoptosis. In G. S. Makowski (Ed.), *Advances in Clinical Chemistry* (Vol. 75, pp. 99-158): Elsevier.

Brand-Williams, W., Cuvelier, M.-E. and Berset, C. (1995). Use of a free radical method to evaluate antioxidant activity. *LWT-Food Science and Technology, 28*(1), 25-30.

Cherng, J.-Y. and Shih, M.-F. (2006). Improving glycogenesis in Streptozocin (STZ) diabetic mice after administration of green algae Chlorella. *Life Sciences, 78*(11), 1181-1186.

Chew, Y., Lim, Y., Omar, M. and Khoo, K. (2008). Antioxidant activity of three edible seaweeds from two areas in South East Asia. *LWT-Food Science and Technology, 41*(6), 1067-1072.

Chin, Y.-W., Balunas, M. J., Chai, H. B. and Kinghorn, A. D. (2006). Drug discovery from natural sources. *The AAPS Journal, 8*(2), E239-E253.

Chu, Y. H., Chang, C. L. and Hsu, H. F. (2000). Flavonoid content of several vegetables and their antioxidant activity. *Journal of the Science of Food and Agriculture, 80*(5), 561-566.

Collins, Q. F., Liu, H.-Y., Pi, J., Liu, Z., Quon, M. J. and Cao, W. (2007). Epigallocatechin-3-gallate (EGCG), a green tea polyphenol, suppresses hepatic gluconeogenesis through 5′-AMP-activated protein kinase. *Journal of Biological Chemistry, 282*(41), 30143-30149.

Cox, P. and Heinrich, M. (2001). Ethnobotanical drug discovery: Uncertainty or promise? *Pharmaceutical News, 8*(3), 55-59.

Cox, P. A. and Balick, M. J. (1994). The ethnobotanical approach to drug discovery. *Scientific American, 270*(6), 82-87.

Cushnie, T. P. T. and Lamb, A. J. (2005). Antimicrobial activity of flavonoids. *International Journal of Antimicrobial Agents, 26*(5), 343-356.

Dahl, G. and Akerud, T. (2013). Pharmacokinetics and the drug–target residence time concept. *Drug Discovery Today, 18*(15), 697-707.

Dal, S., Jeandidier, N., Seyfritz, E., Bietiger, W., Péronet, C., Moreau, F., Sigrist, S. (2016). Featured Article: Oxidative stress status and liver tissue defenses in diabetic rats during intensive subcutaneous insulin therapy. *Experimental Biology and Medicine, 241*(2), 184-192.

Dao, T.-M. A., Waget, A., Klopp, P., Serino, M., Vachoux, C., Pechere, L., Barra, Y. (2011). Resveratrol increases glucose induced GLP-1 secretion in mice: a mechanism which contributes to the glycemic control. *PloS One, 6*(6), e20700.

Das, H., Groh, V., Kuijl, C., Sugita, M., Morita, C. T., Spies, T. and Bukowski, J. F. (2001). MICA engagement by human Vγ2Vδ2 T cells enhances their antigen-dependent effector function. *Immunity, 15*(1), 83-93.

de Bock, M., Derraik, J. G. and Cutfield, W. S. (2012). Polyphenols and glucose homeostasis in humans. *Journal of the Academy of Nutrition and Dietetics, 112*(6), 808-815.

de Zeeuw, P., Wong, B. W. and Carmeliet, P. (2015). Metabolic Adaptations in Diabetic Endothelial Cells. *Circulation Journal, 79*(5), 934-941.

DeGruttola, A. K., Low, D., Mizoguchi, A. and Mizoguchi, E. (2016). Current Understanding of Dysbiosis in Disease in Human and Animal Models. *Inflammatory Bowel Diseases, 22*(5), 1137-1150.

Duan, W., Ji, W., Wei, Y., Zhao, R., Chen, Z., Geng, Y., Wang, X. (2018). Separation and Purification of Fructo-Oligosaccharide by High-Speed Counter-Current Chromatography Coupled with Precolumn Derivatization. *Molecules, 23*(2), 381.

Eberhard, S., Philip, W., Thomas, M. and Andreas, D. (2014). Mitochondrial Redox Signaling: Interaction of Mitochondrial Reactive Oxygen Species with Other Sources of Oxidative Stress. *Antioxidants & Redox Signaling, 20*(2), 308-324.

Eddouks, M., Chattopadhyay, D. and Zeggwagh, N. A. (2012). Animal Models as Tools to Investigate Antidiabetic and Anti-Inflammatory Plants. *Evidence-Based Complementary and Alternative Medicine, 2012*, 14.

Eidi, A., Eidi, M. and Esmaeili, E. (2006). Antidiabetic effect of garlic (Allium sativum L.) in normal and streptozotocin-induced diabetic rats. *Phytomedicine, 13*(9-10), 624-629.

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

Ellman, G. L. (1959). Tissue sulfhydryl groups. *Archives of Biochemistry and Biophysics, 82*(1), 70-77.

Eom, S. H., Lee, S. H., Yoon, N. Y., Jung, W. K., Jeon, Y. J., Kim, S. K., Kim, Y. M. (2012). α-Glucosidase-and α-amylase-inhibitory activities of phlorotannins from Eisenia bicyclis. *Journal of the Science of Food and Agriculture, 92*(10), 2084-2090.

Eyre, H., Kahn, R., Robertson, R. M., Clark, N. G., Doyle, C., Gansler, T., Taubert, K. (2004). Preventing cancer, cardiovascular disease, and diabetes: a common agenda for the American Cancer Society, the American Diabetes Association, and the American Heart Association. *CA: A Cancer Journal for Clinicians, 54*(4), 190-207.

Fairhead, V. A., Amsler, C. D., McClintock, J. B. and Baker, B. J. (2005). Variation in phlorotannin content within two species of brown macroalgae (Desmarestia anceps and D. menziesii) from the Western Antarctic Peninsula. *Polar Biology, 28*(9), 680-686.

Fansheng, K., Zhipeng, S., Xiaoming, G., Feng, Z. and Yongguang, B. (2018). Antidiabetic and Lipid-Lowering Effects of the Polyphenol Extracts from the Leaves of Clausena lansium (Lour.) Skeels on Streptozotocin-Induced Type 2 Diabetic Rats. *Journal of Food Science, 83*(1), 212-220.

Fu, Z., Zhang, W., Zhen, W., Lum, H., Nadler, J., Bassaganya-Riera, J., Liu, D. (2010). Genistein induces pancreatic β-cell proliferation through activation of multiple signaling pathways and prevents insulin-deficient diabetes in mice. *Endocrinology, 151*(7), 3026-3037.

Fukumoto, L. and Mazza, G. (2000). Assessing antioxidant and prooxidant activities of phenolic compounds. *Journal of Agricultural and Food Chemistry, 48*(8), 3597-3604.

Furman, B. L. (2015). Streptozotocin-Induced Diabetic Models in Mice and Rats. *Current Protocols in Pharmacology, 70*(1), 5.47.41-45.47.20.

Furukawa, S., Fujita, T., Shimabukuro, M., Iwaki, M., Yamada, Y., Nakajima, Y., Shimomura, I. (2017). Increased oxidative stress in obesity and its impact on metabolic syndrome. *The Journal of Clinical Investigation, 114*(12), 1752-1761.

Garg, R. and Gupta, G. (2008). Progress in controlled gastroretentive delivery systems. *Tropical Journal of Pharmaceutical Research, 7*(3), 1055-1066.

Gray, S. P., Di Marco, E., Kennedy, K., Chew, P., Okabe, J., El-Osta, A., Jandeleit-Dahm, K. A. M. (2015). Reactive Oxygen Species Can Provide Atheroprotection via NOX4-Dependent Inhibition of Inflammation and Vascular Remodeling. *Arteriosclerosis, Thrombosis, and Vascular Biology, 36*(2):295-307.

Guariguata, L., Whiting, D. R., Hambleton, I., Beagley, J., Linnenkamp, U. and Shaw, J. E. (2014). Global estimates of diabetes prevalence for 2013 and projections for 2035. *Diabetes Research and Clinical Practice, 103*(2), 137-149.

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

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

Hanhineva, K., Törrönen, R., Bondia-Pons, I., Pekkinen, J., Kolehmainen, M., Mykkänen, H. and Poutanen, K. (2010a). Impact of dietary polyphenols on carbohydrate metabolism. *International Journal of Molecular Sciences, 11*(4), 1365-1402.

Hanhineva, K., Törrönen, R., Bondia-Pons, I., Pekkinen, J., Kolehmainen, M., Mykkänen, H. and Poutanen, K. (2010b). Impact of Dietary Polyphenols on Carbohydrate Metabolism. *International Journal of Molecular Sciences, 11*(4), 1365.

Harald, S., Roland, S., Claudia, V., Göran, P., Dennis, R., Andreas, D. and Antonio, C. (2015). Antioxidants in Translational Medicine. *Antioxidants & Redox Signaling, 23*(14), 1130-1143.

Harvey, A. L. (2008). Natural products in drug discovery. *Drug Discovery Today, 13*(19-20), 894-901.

Hecht, F., Pessoa, C. F., Gentile, L. B., Rosenthal, D., Carvalho, D. P. and Fortunato, R. S. (2016). The role of oxidative stress on breast cancer development and therapy. *Tumor Biology, 37*(4), 4281-4291.

Heffernan, N., Brunton, N. P., FitzGerald, R. J. and Smyth, T. J. (2015). Profiling of the molecular weight and structural isomer abundance of macroalgae-derived phlorotannins. *Marine Drugs, 13*(1), 509-528.

Hensley, K., Robinson, K. A., Gabbita, S. P., Salsman, S. and Floyd, R. A. (2000). Reactive oxygen species, cell signaling, and cell injury. *Free Radical Biology and Medicine, 28*(10), 1456-1462.

Heo, S.-J., Hwang, J.-Y., Choi, J.-I., Han, J.-S., Kim, H.-J. and Jeon, Y.-J. (2009). Diphlorethohydroxycarmalol isolated from Ishige okamurae, a brown algae, a potent α-glucosidase and α-amylase inhibitor, alleviates postprandial hyperglycemia in diabetic mice. *European Journal of Pharmacology, 615*(1-3), 252-256.

Hermes-Lima, M. (2004). Oxygen in biology and biochemistry: role of free radicals. *Functional metabolism: Regulation and Adaptation, 1*, 319-366.

Husni, A. and Wijayanti, R. (2014). Inhibitory Activity of [alpha]-Amylase and [alpha]-Glucosidase by Padina pavonica Extracts. *Journal of Biological Sciences, 14*(8), 515.

Hyun, E., Ramachandran, R., Cenac, N., Houle, S., Rousset, P., Saxena, A., Vergnolle, N. (2010). Insulin modulates protease-activated receptor 2 signaling: implications for the innate immune response. *The Journal of Immunology, 184*(5), 2702-2709.

Inzucchi, S. E., Bergenstal, R. M., Buse, J. B., Diamant, M., Ferrannini, E., Nauck, M., Matthews, D. R. (2015). Management of Hyperglycemia in Type 2 Diabetes, 2015: A Patient-Centered Approach: Update to a Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care, 38*(1), 140-149.

Ismail, A. and Hong, T. S. (2002). Antioxidant activity of selected commercial seaweeds. *Malaysian Journal of Nutrition, 8*(2), 167-177.

Iwai, K. (2008). Antidiabetic and antioxidant effects of polyphenols in brown alga Ecklonia stolonifera in genetically diabetic KK-A y mice. *Plant Foods for Human Nutrition, 63*(4), 163.

Izabela, M. and Katarzyna, C. (2015). Algae as production systems of bioactive compounds. *Engineering in Life Sciences, 15*(2), 160-176.

Jabir, N. A. and Ismail, M. M. (2012). *Malaysian Sugar Industry: Is There A Competitive Advantage?* Paper presented at the Proceedings of USM-AUT International Conference 2012 Sustainable Economic Development: Policies and Strategies.

Jadzinsky, M., Pfützner, A., Paz-Pacheco, E., Xu, Z., Allen, E. and Chen, R. (2009). Saxagliptin given in combination with metformin as initial therapy improves glycaemic control in patients with type 2 diabetes compared with either monotherapy: a randomized controlled trial. *Diabetes, Obesity and Metabolism, 11*(6), 611-622.

Jan Mohamed, H. J. B., Yap, R. W. K., Loy, S. L., Norris, S. A., Biesma, R. and Aagaard-Hansen, J. (2015). Prevalence and determinants of overweight, obesity, and type 2 diabetes mellitus in adults in Malaysia. *Asia Pacific Journal of Public Health, 27*(2), 123-135.

Jiang, T., Huang, Z., Lin, Y., Zhang, Z., Fang, D. and Zhang, D. D. (2010). The protective role of Nrf2 in streptozotocin-induced diabetic nephropathy. *Diabetes, 59*(4), 850-860.

Johansen, J. S., Harris, A. K., Rychly, D. J. and Ergul, A. (2005). Oxidative stress and the use of antioxidants in diabetes: linking basic science to clinical practice. *Cardiovascular Diabetology, 4*(1), 5.

Johnston, K., Sharp, P., Clifford, M. and Morgan, L. (2005). Dietary polyphenols decrease glucose uptake by human intestinal Caco-2 cells. *FEBS letters, 579*(7), 1653-1657.

Jung, H. A., Oh, S. H. and Choi, J. S. (2010). Molecular docking studies of phlorotannins from Eisenia bicyclis with BACE1 inhibitory activity. *Bioorganic & Medicinal Chemistry Letters, 20*(11), 3211-3215.

Jung, H. A., Yoon, N. Y., Woo, M.-H. and Choi, J. S. (2008). Inhibitory activities of extracts from several kinds of seaweeds and phlorotannins from the brown alga Ecklonia stolonifera on glucose-mediated protein damage and rat lens aldose reductase. *Fisheries Science, 74*(6), 1363-1365.

Jung, U. J., Lee, M.-K., Jeong, K.-S. and Choi, M.-S. (2004). The hypoglycemic effects of hesperidin and naringin are partly mediated by hepatic glucose-regulating enzymes in C57BL/KsJ-db/db mice. *The Journal of Nutrition, 134*(10), 2499-2503.

Jung, U. J., Lee, M.-K., Park, Y. B., Kang, M. A. and Choi, M.-S. (2006). Effect of citrus flavonoids on lipid metabolism and glucose-regulating enzyme mRNA levels in type-2 diabetic mice. *The International Journal of Biochemistry & Cell Biology, 38*(7), 1134-1145.

Kang, C., Jin, Y. B., Lee, H., Cha, M., Sohn, E.-t., Moon, J., Hong, J.-S. (2010). Brown alga Ecklonia cava attenuates type 1 diabetes by activating AMPK and Akt signaling pathways. *Food and Chemical Toxicology, 48*(2), 509-516.

Kang, M.-C., Wijesinghe, W. A. J. P., Lee, S.-H., Kang, S.-M., Ko, S.-C., Yang, X., .Jeon, Y.-J. (2013). Dieckol isolated from brown seaweed Ecklonia cava attenuates type II diabetes in db/db mouse model. *Food and Chemical Toxicology, 53*, 294-298.

Kang, S.-I., Jin, Y.-J., Ko, H.-C., Choi, S.-Y., Hwang, J.-H., Whang, I., Kim, S.-J. (2008). Petalonia improves glucose homeostasis in streptozotocin-induced diabetic mice. *Biochemical and Biophysical Research Communications, 373*(2), 265-269.

Karthikesan, K., Pari, L. and Menon, V. (2010). Antihyperlipidemic effect of chlorogenic acid and tetrahydrocurcumin in rats subjected to diabetogenic agents. *Chemico-Biological Interactions, 188*(3), 643-650.

Kellogg, J., Grace, M. H. and Lila, M. A. (2014). Phlorotannins from Alaskan seaweed inhibit carbolytic enzyme activity. *Marine Drugs, 12*(10), 5277-5294.

Kim, J.-O., Kim, K.-S., Lee, G.-D. and Kwon, J.-H. (2009). Antihyperglycemic and Antioxidative Effects of New Herbal Formula in Streptozotocin-Induced Diabetic Rats. *Journal of Medicinal Food, 12*(4), 728-735.

Kirchmair, J., Göller, A. H., Lang, D., Kunze, J., Testa, B., Wilson, I. D., Schneider, G. (2015). Predicting drug metabolism: experiment and/or computation? *Nature Reviews Drug Discovery, 14*, 387.

Koivikko, R., Loponen, J., Honkanen, T. and Jormalainen, V. (2005). Contents of soluble, cell-wall-bound and exuded phlorotannins in the brown alga Fucus vesiculosus, with implications on their ecological functions. *Journal of Chemical Ecology, 31*(1), 195-212.

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

Krishnakumar, Issac, A., Nm, J., Ninan, E., Maliakel, B. and Kuttan, R. (2014). Effects of the polyphenol content on the anti-diabetic activity of Cinnamomum zeylanicum extracts. *Food & Function, 5*(9), 2208-2220.

Kumar, R., Balaji, S., Uma, T. and Sehgal, P. (2009). Fruit extracts of Momordica charantia potentiate glucose uptake and up-regulate Glut-4, PPARγ and PI3K. *Journal of Ethnopharmacology, 126*(3), 533-537.

Kumar, V., Abbas, A. K., Fausto, N. and Aster, J. C. (2014). *Robbins and Cotran Pathologic Basis of Disease*, professional edition e-book. Elsevier Health Sciences.

Kumaran, A. (2006). Antioxidant and free radical scavenging activity of an aqueous extract of Coleus aromaticus. *Food Chemistry, 97*(1), 109-114.

Kumari, K. and Augusti, K. (2002). Antidiabetic and antioxidant effects of S-methyl cysteine sulfoxide isolated from onions (Allium cepa Linn) as compared to standard drugs in alloxan diabetic rats.

Kumazawa, S., Taniguchi, M., Suzuki, Y., Shimura, M., Kwon, M.-S. and Nakayama, T. (2002). Antioxidant activity of polyphenols in carob pods. *Journal of Agricultural and Food Chemistry, 50*(2), 373-377.

Lee, Y. L., Huang, G. W., Liang, Z. C., & Mau, J. L. (2007). Antioxidant properties of three extracts from Pleurotus citrinopileatus. *LWT-Food Science and Technology*, 40(5), 823-833.

Lee, S.-H., Han, J.-S., Heo, S.-J., Hwang, J.-Y. and Jeon, Y.-J. (2010). Protective effects of dieckol isolated from Ecklonia cava against high glucose-induced oxidative stress in human umbilical vein endothelial cells. *Toxicology in Vitro, 24*(2), 375-381.

Lee, S.-H. and Jeon, Y.-J. (2013). Anti-diabetic effects of brown algae derived phlorotannins, marine polyphenols through diverse mechanisms. *Fitoterapia, 86*, 129-136.

Lee, S.-H., Min, K.-H., Han, J.-S., Lee, D.-H., Park, D.-B., Jung, W.-K., Jeon, Y.-J. (2012). Effects of brown alga, Ecklonia cava on glucose and lipid metabolism in C57BL/KsJ-db/db mice, a model of type 2 diabetes mellitus. *Food and Chemical Toxicology, 50*(3-4), 575-582.

Lee, S. H., Karadeniz, F., Kim, M. M. and Kim, S. K. (2009). α-Glucosidase and α-amylase inhibitory activities of phloroglucinal derivatives from edible marine brown alga, Ecklonia cava. *Journal of the Science of Food and Agriculture, 89*(9), 1552-1558.

Lei, X. G., Zhu, J.-H., Cheng, W.-H., Bao, Y., Ho, Y.-S., Reddi, A. R., Arnér, E. S. J. (2016). Paradoxical Roles of Antioxidant Enzymes: Basic Mechanisms and Health Implications. *Physiological Reviews, 96*(1), 307-364.

Letchuman, G., Wan Nazaimoon, W., Wan Mohamad, W., Chandran, L., Tee, G., Jamaiyah, H., Ahmad Faudzi, Y. (2010). Prevalence of diabetes in the Malaysian national health morbidity survey III 2006. *Medical Journal of Malaysia, 65*(3), 180-186.

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

Li, R., Liang, T., Xu, L., Li, Y., Zhang, S. and Duan, X. (2013). Protective effect of cinnamon polyphenols against STZ-diabetic mice fed high-sugar, high-fat diet and its underlying mechanism. *Food and Chemical Toxicology, 51*, 419-425.

Li, X. L., Xu, G., Chen, T., Wong, Y. S., Zhao, H. L., Fan, R. R., Chan, J. C. N. (2009b). Phycocyanin protects INS-1E pancreatic beta cells against human islet amyloid polypeptide-induced apoptosis through attenuating oxidative stress and modulating JNK and p38 mitogen-activated protein kinase pathways. *The International Journal of Biochemistry & Cell Biology, 41*(7), 1526-1535.

Li, Y.-X., Wijesekara, I., Li, Y. and Kim, S. K. (2011). Phlorotannins as bioactive agents from brown algae. *Process Biochemistry, 46*(12), 2219-2224.

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

Li, Y., Qian, Z.-J., Ryu, B., Lee, S.-H., Kim, M.-M. and Kim, S. K. (2009c). Chemical components and its antioxidant properties in vitro: an edible marine brown alga, Ecklonia cava. *Bioorganic & Medicinal Chemistry, 17*(5), 1963-1973.

Lipnick, R., Cotruvo, J., Hill, R., Bruce, R., Stitzel, K., Walker, A. P., Springer, J. (1995). Comparison of the up-and-down, conventional LD50, and fixed-dose acute toxicity procedures. *Food and Chemical Toxicology, 33*(3), 223-231.

Louis, S. F. and Zahradka, P. (2010). Vascular smooth muscle cell motility: From migration to invasion. *Experimental & Clinical Cardiology, 15*(4), e75-e85.

Lv, Y. (2016). Triterpenes and phenolic compounds in apple fruit (Malus domestica Borkh.). Vol. 2016, No. 5.

Ma, J., Jin, X., Yang, L. and Liu, Z.-L. (2004). Diarylheptanoids from the rhizomes of Zingiber officinale. *Phytochemistry, 65*(8), 1137-1143.

Mahendranath G., Shaik, A. B., Jamuna, J. B., Paramahans, V. S., Ummiti, J. S., Prasada R. (2015). Anti-diabetic effect of dietary mango (Mangifera indica L.) peel in streptozotocin-induced diabetic rats. *Journal of the Science of Food and Agriculture, 95*(5), 991-999.

Manach, C., Scalbert, A., Morand, C., Rémésy, C. and Jiménez, L. (2004). Polyphenols: food sources and bioavailability. *The American Journal of Clinical Nutrition, 79*(5), 727-747.

Mandal, S. C., Mandal, V. and Das, A. K. (2015). *Essentials of botanical extraction: principles and applications*. Academic Press.

Manivannan, J., Silambarasan, T., Shanthakumar, J., Suganya, N. and Kanchana, S. (2016). Role of Antioxidants in Human Health. In M. V. Hegde, A. A. Zanwar, & S. P. Adekar (Eds.), *Omega-3 Fatty Acids: Keys to Nutritional Health* (pp. 501-512). Cham: Springer International Publishing.

Maritim, A., Sanders, a. and Watkins, J., 3rd. (2003). Diabetes, oxidative stress, and antioxidants: a review. *Journal of Biochemical and Molecular Toxicology, 17*(1), 24-38.

Masuda, Y., Kikuzaki, H., Hisamoto, M. and Nakatani, N. (2004). Antioxidant properties of gingerol related compounds from ginger. *Biofactors, 21*(1-4), 293-296.

Mathers, C. D. and Loncar, D. (2006). Projections of Global Mortality and Burden of Disease from 2002 to 2030. *PLoS Medicine, 3*(11), e442.

McDougall, G. J., Shpiro, F., Dobson, P., Smith, P., Blake, A. and Stewart, D. (2005). Different polyphenolic components of soft fruits inhibit α-amylase and α-glucosidase. *Journal of Agricultural and Food Chemistry, 53*(7), 2760-2766.

Min, K.-H., Kim, H.-J., Jeon, Y.-J. and Han, J.-S. (2011). Ishige okamurae ameliorates hyperglycemia and insulin resistance in C57BL/KsJ-db/db mice. *Diabetes Research and Clinical Practice, 93*(1), 70-76.

Misra, M. K., Sarwat, M., Bhakuni, P., Tuteja, R. and Tuteja, N. (2009). Oxidative stress and ischemic myocardial syndromes. *Medical Science Monitor, 15*(10), RA209-RA219.

Moron, M. S., Depierre, J. W. and Mannervik, B. (1979). Levels of glutathione, glutathione reductase and glutathione S-transferase activities in rat lung and liver. *Biochimica et Biophysica Acta (BBA)-General Subjects, 582*(1), 67-78.

Motshakeri, M., Ebrahimi, M., Goh, Y. M., Othman, H. H., Hair-Bejo, M. and Mohamed, S. (2014). Effects of Brown Seaweed (Sargassum polycystum) Extracts on Kidney, Liver, and Pancreas of Type 2 Diabetic Rat Model. *Evidence-Based Complementary and Alternative Medicine, 2014*, 11.

Münzel, T., Gori, T., Keaney, J. J. F., Maack, C. and Daiber, A. (2015). Pathophysiological role of oxidative stress in systolic and diastolic heart failure and its therapeutic implications. *European Heart Journal, 36*(38), 2555-2564.

Murugan, A. C., Karim, M. R., Yusoff, M. B. M., Tan, S. H., Asras, M. F. B. F. and Rashid, S. S. (2015a). New insights into seaweed polyphenols on glucose homeostasis. *Pharmaceutical Biology, 53*(8), 1087-1097.

Murugan, A. C., Vallal, D., Karim, M. R., Govindan, N., Yusoff, M. B. M. and Rahman, M. M. (2015b). Journal of Chemical and Pharmaceutical Research, 2015, 7 (8): 355-362. *Journal of Chemical and Pharmaceutical Research, 7*(8), 355-362.

Nasri, H., Nematbakhsh, M., Ghobadi, S., Ansari, R., Shahinfard, N. and Rafieian-kopaei, M. (2013). Preventive and Curative Effects of Ginger Extract Against Histopathologic Changes of Gentamicin-Induced Tubular Toxicity in Rats. *International Journal of Preventive Medicine, 4*(3), 316-321.

Neuser, D., Benson, A., Brückner, A., Goldberg, R. B., Hoogwerf, B. J. and Petzinna, D. (2005). Safety and tolerability of acarbose in the treatment of type 1 and type 2 diabetes mellitus. *Clinical Drug Investigation, 25*(9), 579-587.

Ng, M., Fleming, T., Robinson, M., Thomson, B., Graetz, N., Margono, C., Abera, S. F. (2014). Global, regional, and national prevalence of overweight and obesity in children and adults during 1980–2013: a systematic analysis for the Global Burden of Disease Study 2013. *The Lancet, 384*(9945), 766-781.

Ni-Ni-Win, Hanyuda, T., Draisma, S. G., Furnari, G., Meinesz, A. and Kawai, H. (2011). Padina ditristromatica sp. nov. and Padina pavonicoides sp. nov.(Dictyotales, Phaeophyceae), two new species from the Mediterranean Sea based on morphological and molecular markers. *European Journal of Phycology, 46*(4), 327-341.

Niehaus, W. and Samuelsson, B. (1968). Formation of malonaldehyde from phospholipid arachidonate during microsomal lipid peroxidation. *The FEBS Journal, 6*(1), 126-130.

Nor, M., Safiza, N., Khor, G. L., Shahar, S., Kee, C. C., Haniff, J., Zainuddin, A. A. (2008). The Third National Health and Morbidity Survey (NHMS III) 2006: nutritional status of adults aged 18 years and above. *Malaysian Journal of Nutrition, 14*(2), 1-87.

Nwosu, F., Morris, J., Lund, V. A., Stewart, D., Ross, H. A. and McDougall, G. J. (2011). Anti-proliferative and potential anti-diabetic effects of phenolic-rich extracts from edible marine algae. *Food Chemistry, 126*(3), 1006-1012.

Ogawa, H., Nakayama, M., Morimoto, T. and et al. (2008). Low-dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes: A randomized controlled trial. *JAMA, 300*(18), 2134-2141.

Okada, Y., Ishimaru, A., Suzuki, R. and Okuyama, T. (2004). A new phloroglucinol derivative from the brown alga Eisenia bicyclis: potential for the effective

treatment of diabetic complications. *Journal of Natural Products, 67*(1), 103-105.

Omara, E. A., Nada, S. A., Farrag, A. R. H., Sharaf, W. M. and El-Toumy, S. A. (2012). Therapeutic effect of Acacia nilotica pods extract on streptozotocin induced diabetic nephropathy in rat. *Phytomedicine, 19*(12), 1059-1067.

Organization, W. H. (2009). Fact sheet No. 312: Diabetes. *Geneva: WHO*.

Othman, A., Ismail, A., Ghani, N. A. and Adenan, I. (2007). Antioxidant capacity and phenolic content of cocoa beans. *Food Chemistry, 100*(4), 1523-1530.

Oudemans-van Straaten, H. M., Man, A. M. S.-d. and de Waard, M. C. (2014). Vitamin C revisited. *Critical Care, 18*(4), 460.

Owu, D. U., Nwokocha, C. R., Ikpi, D. E. and Ogar, E. I. (2016). Effect of vitamin C supplementation on platelet aggregation and serum electrolytes levels in streptozotocin-induced diabetes mellitus in rats. *Nigerian Journal of Physiological Sciences, 31*(1), 55-61.

Pantidos, N., Boath, A., Lund, V., Conner, S. and McDougall, G. J. (2014). Phenolic-rich extracts from the edible seaweed, ascophyllum nodosum, inhibit α-amylase and α-glucosidase: Potential anti-hyperglycemic effects. *Journal of Functional Foods, 10*, 201-209.

Pari, L., Karthikeyan, A., Karthika, P. and Rathinam, A. (2015). Protective effects of hesperidin on oxidative stress, dyslipidaemia and histological changes in iron-induced hepatic and renal toxicity in rats. *Toxicology Reports, 2*, 46-55.

Park, C. E., Kim, M.-J., Lee, J. H., Min, B.-I., Bae, H., Choe, W., Ha, J. (2007). Resveratrol stimulates glucose transport in C2C12 myotubes by activating AMP-activated protein kinase. *Experimental & Molecular Medicine, 39*(2), 222.

Park, J., Choe, S. S., Choi, A. H., Kim, K. H., Yoon, M. J., Suganami, T., Kim, J. B. (2006). Increase in glucose-6-phosphate dehydrogenase in adipocytes stimulates oxidative stress and inflammatory signals. *Diabetes, 55*(11), 2939-2949.

Parmar, S. S., Jaiwal, A., Dhankher, O. P. and Jaiwal, P. K. (2015). Coenzyme Q10 production in plants: current status and future prospects. *Critical Reviews in Biotechnology, 35*(2), 152-164.

Patia, M., Das Sharma, S., Nayaka, L. and Pandab, C. (2016). Uses of seaweed and its application to human welfare: a review. *International Journal of Pharmacy and Pharmaceutical Sciences, 8*, 12-20.

Pedraza-Chaverrí, J., Maldonado, P. D., Medina-Campos, O. N., Olivares-Corichi, I. M., de los Ángeles Granados-Silvestre, M. a., Hernández-Pando, R. and Ibarra-Rubio, M. a. E. (2000). Garlic ameliorates gentamicin nephrotoxicity: relation to antioxidant enzymes. *Free Radical Biology and Medicine, 29*(7), 602-611.

Pereira, D. M., Valentão, P., Pereira, J. A. and Andrade, P. B. (2009). Phenolics: From chemistry to biology: Molecular Diversity Preservation International.

Pérez-Jiménez, J., Neveu, V., Vos, F. and Scalbert, A. (2010). Systematic analysis of the content of 502 polyphenols in 452 foods and beverages: an application of the phenol-explorer database. *Journal of Agricultural and Food Chemistry, 58*(8), 4959-4969.

Perry, R. J., Samuel, V. T., Petersen, K. F. and Shulman, G. I. (2014). The role of hepatic lipids in hepatic insulin resistance and type 2 diabetes. *Nature, 510*, 84.

Phuong, M., Ali, B., Aziz, E., Abdellatif, S., Yahia, C. and Pierre, S. (2004). The petroleum ether extract of Nigella sativa exerts lipid lowering and insulin-sensitizing action in the rats. *Journal of Ethnopharmacology, 94*, 251-259.

Pisoschi, A. M. and Pop, A. (2015). The role of antioxidants in the chemistry of oxidative stress: A review. *European Journal of Medicinal Chemistry, 97*, 55-74.

Prabhakar, P. K. and Doble, M. (2009). Synergistic effect of phytochemicals in combination with hypoglycemic drugs on glucose uptake in myotubes. *Phytomedicine, 16*(12), 1119-1126.

Ragan, M. A. (1986). Phlorotannins, brown algal polyphenols. *Progress in Phycological Research, 4*, 177-241.

Rahman, K. (2007). Studies on free radicals, antioxidants, and co-factors. *Clinical Interventions in Aging, 2*(2), 219.

Ramnanan, C., Edgerton, D., Kraft, G. and Cherrington, A. (2011). Physiologic action of glucagon on liver glucose metabolism. *Diabetes, Obesity and Metabolism, 13*(s1), 118-125.

Rangel-Huerta, O. D., Aguilera, C. M., Martin, M. V., Soto, M. J., Rico, M. C., Vallejo, F., Mesa, M. D. (2015). Normal or High Polyphenol Concentration in Orange Juice Affects Antioxidant Activity, Blood Pressure, and Body Weight in Obese or Overweight Adults. *The Journal of Nutrition, 145*(8), 1808-1816.

Rolf, T., X., Q. S., Dang, X. T. and Vincent, L. (2011). Kava and Kava Hepatotoxicity: Requirements for Novel Experimental, Ethnobotanical and Clinical Studies Based on a Review of the Evidence. *Phytotherapy Research, 25*(9), 1263-1274.

Saha, A., Pawar, V. and Jayaraman, S. (2012). Characterisation of polyphenols in Terminalia arjuna bark extract. *Indian Journal of Pharmaceutical Sciences, 74*(4), 339.

Sarnak, M. J., Levey, A. S., Schoolwerth, A. C., Coresh, J., Culleton, B., Hamm, L. L., Wilson, P. W. (2003). Kidney Disease as a Risk Factor for Development of Cardiovascular Disease. A Statement From the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. *Circulation, 108*(17), 2154-2169.

Seidell, J. C. (2000). Obesity, insulin resistance and diabetes - a worldwide epidemic. *British Journal of Nutrition, 83*(S1), S5-S8.

Serreze, D. V., Niens, M., Kulik, J. and DiLorenzo, T. P. (2016). Bridging Mice to Men: Using HLA Transgenic Mice to Enhance the Future Prediction and Prevention of Autoimmune Type 1 Diabetes in Humans. *Mouse Models for Drug Discovery: Methods and Protocols*, 137-151.

Shargel, L., Andrew, B. and Wu-Pong, S. (2015). *Applied biopharmaceutics & pharmacokinetics*. McGraw-Hill Medical Publishing Division.

Shibata, T., Ishimaru, K., Kawaguchi, S., Yoshikawa, H. and Hama, Y. (2008). Antioxidant activities of phlorotannins isolated from Japanese Laminariaceae. *Journal of Applied Phycology, 20*(5), 705.

Shibata, T., Kawaguchi, S., Hama, Y., Inagaki, M., Yamaguchi, K. and Nakamura, T. (2004). Local and chemical distribution of phlorotannins in brown algae. *Journal of Applied Phycology, 16*(4), 291-296.

Shibata, T., Miyasaki, T., Miyake, H., Tanaka, R. and Kawaguchi, S. (2014). The Influence of Phlorotannins and Bromophenols on the Feeding Behavior of Marine Herbivorous Gastropod <i>Turbo cornutus</i&gt. *American Journal of Plant Sciences, Vol.05No.03*, 6.

Shibata, T., Nagayama, K., Tanaka, R., Yamaguchi, K. and Nakamura, T. (2003). Inhibitory effects of brown algal phlorotannins on secretory phospholipase A2s, lipoxygenases and cyclooxygenases. *Journal of Applied Phycology, 15*(1), 61-66.

Shibata, T., Yamaguchi, K., Nagayama, K., Kawaguchi, S. and Nakamura, T. (2002). Inhibitory activity of brown algal phlorotannins against glycosidases from the viscera of the turban shell Turbo cornutus. *European Journal of Phycology, 37*(4), 493-500.

Singh, N. and Rajini, P. (2004). Free radical scavenging activity of an aqueous extract of potato peel. *Food Chemistry, 85*(4), 611-616.

Sinha, A. K. (1972). Colorimetric assay of catalase. *Analytical Biochemistry, 47*(2), 389-394.

Snyder, S. M., Zhao, B., Luo, T., Kaiser, C., Cavender, G., Hamilton-Reeves, J., Shay, N. F. (2016). Consumption of Quercetin and Quercetin-Containing Apple and Cherry Extracts Affects Blood Glucose Concentration, Hepatic Metabolism, and Gene Expression Patterns in Obese C57BL/6J High Fat–Fed Mice. *The Journal of Nutrition, 146*(5), 1001-1007.

Solanki, N. D. and Bhavsar, S. K. (2015). An evaluation of the protective role of Ficus racemosa Linn. in streptozotocin-induced diabetic neuropathy with neurodegeneration. *Indian Journal of Pharmacology, 47*(6), 610-615.

Song, M. Y., Kang, S. Y., Kang, A., Hwang, J. H., Park, Y.-K. and Jung, H. W. (2017). Cinnamomum cassia Prevents High-Fat Diet-Induced Obesity in Mice through the Increase of Muscle Energy. *The American Journal of Chinese Medicine, 45*(05), 1017-1031.

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

Sung-Hwan, E., Sang-Hoon, L., Na-Young, Y., Won-Kyo, J., You-Jin, J., Se-Kwon, K., Young-Mog, K. (2012). α-Glucosidase- and α-amylase-inhibitory activities of phlorotannins from Eisenia bicyclis. *Journal of the Science of Food and Agriculture, 92*(10), 2084-2090.

Svedström, U., Vuorela, H., Kostiainen, R., Laakso, I. and Hiltunen, R. (2006). Fractionation of polyphenols in hawthorn into polymeric procyanidins, phenolic acids and flavonoids prior to high-performance liquid chromatographic analysis. *Journal of Chromatography A, 1112*(1-2), 103-111.

Szablewski, L. (2011). ***Glucose homeostasis and insulin resistance***. Bentham Science Publishers.

Szkudelski, T. and Szkudelska, K. (2011). Anti-diabetic effects of resveratrol. *Annals of the New York Academy of Sciences, 1215*(1), 34-39.

Terpinc, P., Čeh, B., Ulrih, N. P. and Abramovič, H. (2012). Studies of the correlation between antioxidant properties and the total phenolic content of different oil cake extracts. *Industrial Crops and Products, 39*, 210-217.

Testa, R., Bonfigli, A., Genovese, S., De Nigris, V. and Ceriello, A. (2016). The Possible Role of Flavonoids in the Prevention of Diabetic Complications. *Nutrients, 8*(5), 310.

Thakur, P., Kumar, A. and Kumar, A. (2017). Targeting oxidative stress through antioxidants in diabetes mellitus. *Journal of Drug Targeting*, 1-11.

Thomas, N. V. and Kim, S.-K. (2011). Potential pharmacological applications of polyphenolic derivatives from marine brown algae. *Environmental Toxicology and Pharmacology, 32*(3), 325-335.

Titlyanov, E. and Titlyanova, T. (2012). Marine plants of the Asian Pacific region countries, their use and cultivation. *Dalnauka and AV Zhirmunsky Institute of Marine Biology, Far East Branch of the Russian Academy of Sciences, Vladivostok.*

Towler, M. C. and Hardie, D. G. (2007). AMP-activated protein kinase in metabolic control and insulin signaling. *Circulation Research, 100*(3), 328-341.

Tripathi, V., Pandey, V., Udupa, K. and Ru, G. (1992). Arjunolitin, a triterpene glycoside fromTerminalia arjuna. *Phytochemistry, 31*(1), 349-351.

Tsuneki, H., Ishizuka, M., Terasawa, M., Wu, J.-B., Sasaoka, T. and Kimura, I. (2004). Effect of green tea on blood glucose levels and serum proteomic patterns in diabetic (db/db) mice and on glucose metabolism in healthy humans. *BMC Pharmacology, 4*(1), 18.

Turan, A. and Celik, I. (2016). Antioxidant and hepatoprotective properties of dried fig against oxidative stress and hepatotoxicity in rats. *International Journal of Biological Macromolecules, 91*, 554-559.

Umeno, A., Horie, M., Murotomi, K., Nakajima, Y. and Yoshida, Y. (2016). Antioxidative and antidiabetic effects of natural polyphenols and isoflavones. *Molecules, 21*(6), 708.

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

van Duynhoven, J., Vaughan, E. E., Jacobs, D. M., A. Kemperman, R., van Velzen, E. J. J., Gross, G., Van de Wiele, T. (2011). Metabolic fate of polyphenols in the human superorganism. *Proceedings of the National Academy of Sciences, 108*(Supplement 1), 4531-4538.

Vincent, A. M., Russell, J. W., Low, P. and Feldman, E. L. (2004). Oxidative stress in the pathogenesis of diabetic neuropathy. *Endocrine Reviews, 25*(4), 612-628.

Vivekananthan, D. P., Penn, M. S., Sapp, S. K., Hsu, A. and Topol, E. J. (2003). Use of antioxidant vitamins for the prevention of cardiovascular disease: meta-analysis of randomised trials. *The Lancet, 361*(9374), 2017-2023.

Waltner-Law, M. E., Wang, X. L., Law, B. K., Hall, R. K., Nawano, M. and Granner, D. K. (2002). Epigallocatechin gallate, a constituent of green tea, represses hepatic glucose production. *Journal of Biological Chemistry, 277*(38), 34933-34940.

Wang, T., Jónsdóttir, R., Liu, H., Gu, L., Kristinsson, H. G., Raghavan, S. and Ólafsdóttir, G. (2012). Antioxidant Capacities of Phlorotannins Extracted from the Brown Algae Fucus vesiculosus. *Journal of Agricultural and Food Chemistry, 60*(23), 5874-5883.

Wang, T., Jonsdottir, R. and Ólafsdóttir, G. (2009). Total phenolic compounds, radical scavenging and metal chelation of extracts from Icelandic seaweeds. *Food Chemistry, 116*(1), 240-248.

Wei, D., Li, J., Shen, M., Jia, W., Chen, N., Chen, T., Dai, Y. (2010). Cellular Production of n-3 PUFAs and Reduction of n-6–to–n-3 Ratios in the Pancreatic β-Cells and Islets Enhance Insulin Secretion and Confer Protection Against Cytokine-Induced Cell Death. *Diabetes, 59*(2), 471-478.

Wijesinghe, W. and Jeon, Y.-J. (2012). Enzyme-assistant extraction (EAE) of bioactive components: a useful approach for recovery of industrially important metabolites from seaweeds: a review. *Fitoterapia, 83*(1), 6-12.

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

Wojdyło, A., Oszmiański, J. and Czemerys, R. (2007). Antioxidant activity and phenolic compounds in 32 selected herbs. *Food Chemistry, 105*(3), 940-949.

Yamamoto, Y. and Gaynor, R. B. (2001). Therapeutic potential of inhibition of the NF-κB pathway in the treatment of inflammation and cancer. *The Journal of Clinical Investigation, 107*(2), 135-142.

Yang, H., Protiva, P., Cui, B., Ma, C., Baggett, S., Hequet, V., Kennelly, E. J. (2003). New Bioactive Polyphenols from Theobroma g randiflorum ("Cupuaçu"). *Journal of Natural Products, 66*(11), 1501-1504.

Yoon, K.-H., Lee, J.-H., Kim, J.-W., Cho, J. H., Choi, Y.-H., Ko, S.-H., Son, H.-Y. (2006). Epidemic obesity and type 2 diabetes in Asia. *The Lancet, 368*(9548), 1681-1688.

Zang, M., Xu, S., Maitland-Toolan, K. A., Zuccollo, A., Hou, X., Jiang, B., Cohen, R. A. (2006). Polyphenols stimulate AMP-activated protein kinase, lower lipids, and inhibit accelerated atherosclerosis in diabetic LDL receptor–deficient mice. *Diabetes, 55*(8), 2180-2191.

Zhang, B., Kang, M., Xie, Q., Xu, B., Sun, C., Chen, K. and Wu, Y. (2010). Anthocyanins from Chinese bayberry extract protect β cells from oxidative stress-mediated injury via HO-1 upregulation. *Journal of Agricultural and Food Chemistry, 59*(2), 537-545.

Zhang, H. and Tsao, R. (2016). Dietary polyphenols, oxidative stress and antioxidant and anti-inflammatory effects. *Current Opinion in Food Science, 8*, 33-42.

Zhang, J., Tiller, C., Shen, J., Wang, C., Girouard, G. S., Dennis, D., Ewart, H. S. (2007). Antidiabetic properties of polysaccharide-and polyphenolic-enriched fractions from the brown seaweed Ascophyllum nodosum. *Canadian Journal of Physiology And Pharmacology, 85*(11), 1116-1123.

Zhang, S., Zheng, L., Xu, L., Sun, H., Li, H., Yao, J., Peng, J. (2012). Subchronic toxicity study of the total flavonoids from Rosa laevigata Michx fruit in rats. *Regulatory Toxicology and Pharmacology, 62*(2), 221-230.