UNIVERSITI PUTRA MALAYSIA

EFFECTS OF Ficus deltoidea JACK AND VITEXIN ON PANCREAS, BRAIN, KIDNEY AND BONE OF STREPTOZOTOCIN-INDUCED DIABETIC RATS

NURDIANA BINTI SAMSULRIZAL

FPV 2018 16

EFFECTS OF *Ficus deltoidea* JACK AND VITEXIN ON PANCREAS, BRAIN, KIDNEY AND BONE OF STREPTOZOTOCIN-INDUCED DIABETIC RATS

By

NURDIANA BINTI SAMSULRIZAL

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

November 2017

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

EFFECTS OF *Ficus deltoidea* JACK AND VITEXIN ON PANCREAS, BRAIN, KIDNEY AND BONE OF STREPTOZOTOCIN-INDUCED DIABETIC RATS

By

NURDIANA BINTI SAMSULRIZAL

November 2017

Chairman : Goh Yong Meng, PhD
Faculty : Veterinary Medicine

Hyperglycaemia is the predominant cause of tissue damage and other systemic complications through oxidative stress. In diabetic patients, hyperglycaemia is associated with dearrangement of glycemic control. Limiting oxidative stress injuries using antioxidants therefore would be a logical approach to reduce hyperglycaemia and prevent further diabetes complications. *Ficus deltoidea* is a plant high in antioxidant compound content such as vitexin. Improvements in fasting blood glucose and antioxidant activities have indeed been reported following treatment with *F. deltoidea* and vitexin. However, the potential of *F. deltoidea* and vitexin in delaying diabetes-related complications remains to be examined. In this regard, the study aimed to examine the effects of *F. deltoidea* and vitexin on the pancreas, brain, kidney and bone of streptozotocin (STZ)-treated rats. Intraperitoneal injection of STZ (60 mg/kg) was used to induce hyperglycaemia in rats. Methanol extract of *F. deltoidea* and vitexin was then given by oral-gavage for eight weeks. The effects of *F. deltoidea* and vitexin on the pancreas, brain, kidney and bone were further evaluated in four interlinked experiments. The novelty of this study is that Fourier transform infrared (FT-IR) spectroscopy has been introduced as a diagnostic approach to examine metabolic fingerprinting related to the tissue changes showing by biochemical and histological analysis, Morris Water Maze (MWM) test, micro-computed tomography (micro-CT) and fatty acid profiles. The present study demonstrates, for the first time, that *F. deltoidea* treatment was able to preserve pancreatic islet structure, improve learning and memory ability, mitigate renal injury and prevent bone loss in STZ-treated rats. It was also found that *F. deltoidea* resulted in a significant reduction in circulating amylin and an increase in serum insulin and osteocalcin levels. Additionally, the results showed that *F. deltoidea* treatment was associated with increased pancreatic, brain and

kidney antioxidant activity. Although structural and functional improvement of the pancreas and brain was seen, vitexin treatment is associated with an increased risk of acute kidney injury and osteopenia. This might be explained by an increased serum fructose. In conclusion, *F. deltoidea* increased insulin secretion, in part, by reversing STZ-induced organ damage in the pancreas, brain, kidney and bone of rats. This could be related to the optimization of oxidant-antioxidant balance in the tissue.

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

KESAN *Ficus deltoidea* JACK DAN VITEXIN PADA PANKREAS, OTAK, BUAH PINGGANG DAN TULANG TIKUS DIABETIK ARUHAN STREPTOZOTOCIN

Oleh

NURDIANA BINTI SAMSULRIZAL

November 2017

Pengerusi : Goh Yong Meng, PhD
Fakulti : Perubatan Veterinar

Umum mengetahui bahawa hiperglikemia merupakan faktor utama kerosakan tisu dan komplikasi sistemik melalui pengaktifan tekanan oksidatif. Hiperglikemia pada pesakit diabetes lazimnya dikaitkan dengan gangguan metabolisme glukosa. Oleh itu, meminimakan kerosakan tisu melalui rawatan antioksidan berkemungkinan mampu mengurangkan hiperglikemia dan mencegah komplikasi diabetes lanjut. *F. deltoidea* adalah tumbuhan yang kaya kandungan bahan antioksidan seperti vitexin. Kajian terdahulu menunjukkan penggunaan *F. deltoidea* dan vitexin telah berjaya mengurangkan kandungan glukosa darah dan meningkatkan aktiviti antioksida pada model haiwan. Walau bagaimanapun, potensi rawatan *F. deltoidea* dan vitexin untuk mencegah komplikasi yang berkaitan dengan diabetes masih perlu dikaji. Sehubungan itu, kajian ini bertujuan untuk menilai kesan penggunaan *F. deltoidea* dan vitexin pada tisu pankreas, otak, buah pinggang and tulang tikus diabetik aruhan streptozotocin (STZ). Model tikus diaruh menggunakan suntikan intraperitoneal STZ pada dos 60 mg/kg. Rawatan *F. deltoidea* dan vitexin kemudiannya diberikan selama lapan minggu berturut-turut melalui kaedah suap paksa. Kesan rawatan *F. deltoidea* dan vitexin pada tisu pankreas, otak, buah pinggang dan tulang dinilai melalui empat eksperimen berangkai. Uniknya, spektroskopi Fourier transform infrared (FT-IR) digunakapakai sebagai pendekatan baru untuk mengesan pengenalan metabolik bersangkutan dengan perubahan yang diperoleh dari analisa biokimia dan histologi, Morris water maze (MWM), tomografi mikro-komputer (mikro-CT) dan profil asid lemak. Hasil kajian menunjukkan bahawa rawatan *F. deltoidea* boleh memelihara struktur pankreas, meningkatkan keupayaan pembelajaran dan ingatan, mengurangkan kecederaan buah pinggang dan mencegah hakisan tulang dalam tikus-tikus aruhan STZ. Rawatan ini juga didapati berupaya mengurangkan aras amylin serta

meningkatkan kepekatan insulin dan osteocalcin dalam serum. Selain itu, rawatan *F. deltoidea* didapati mampu meningkatkan aktiviti antioksidan pada tisu pankreas, otak dan buah pinggang. Walaupun terdapat perubahan positif pada struktur serta fungsi pankreas dan otak, rawatan vitexin berisiko meningkatkan kegagalan buah pinggang dan osteopenia. Ini berkait rapat dengan kandungan fruktosa yang tinggi dalam serum. Secara konklusinya, peningkatkan rembesan insulin dalam tikus yang terawat-*F. deltoidea* dipengaruhi oleh pemulihan tisu pankreas, otak, buah pinggang dan tulang. Perubahan ini mempunyai kaitan dengan pengoptimalan keseimbangan oksidan-antioksidan dalam tisu.

ACKNOWLEDGEMENTS

Alhamdulillah all praise to Allah, the journey has finally come to the end. The years have been nothing but extraordinary. First and foremost, my sincere appreciation goes to my supervisor Associate Professor Dr Goh Yong Meng for his generosity, a calming spirit, patient motivation and thoughtful discussions. His expertise allowed me to have a broader view on many topics. Thank you for the wonderful journey experience.

I am very much indebted to both Associate Professor Dr Sulaiman Md Dom and Dr Hafandi Ahmad, who were members of my supervisory committee, for their intellectual guidance, advice, comments and suggestion. My sincere appreciation goes to Dr Mahdi Ebrahimi for his constant guidance, encouragement and excellent attention to detail.

I would like to convey my gratitude to the staffs in Physiology Laboratory at Faculty of Veterinary Medicine, Universiti Putra Malaya and Faculty of Applied Sciences, Universiti Teknologi MARA for the use of facilities and technical assistance. Also, thanks to the staffs in Laboratory Animal Facility and Management (LAFAM), Universiti Teknologi MARA for the postoperative care of the animals.

I wish to express my sincere gratitude to Institute of Research Management and Innovation, Universiti Teknologi MARA for the unlimited assistance from their staffs. Financial support from the Ministry of Science, Technology and Innovation (SF: 100-RMI/SF 16/6/2 (7/2015) and Ministry of Higher Education (MOE FRGS: 600-RMI/FRGS 5/3 (5/2014) are gratefully acknowledged.

I would like to extend my deepest appreciation to my friends who have buoyed me, added value to my thinking, invaluable guidance and help. I am particularly indebted to Nurul 'Izzati Shafie, Nur Syimal'ain Azmi, Noor Syaffinaz Noor Mohamad Zin, Nur Farhana Ahmad Sopian and Nur Ajeerah Suhaimi.

Last but not least, I would to thanks my dear husband and my family members for their unwavering support, enduring love, compassion and immeasurable sacrifice. To my daughter, Hajar Amani and my son, Muhammad Naiem, thank you for being amazing and understanding kids. Mama always thanks Allah for both of you.

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

Goh Yong Meng, PhD
Associate Professor
Faculty of Veterinary Medicine
Universiti Putra Malaysia
(Chairman)

Sulaiman Md Dom, PhD
Associate Professor
Faculty of Health Sciences
UiTM Puncak Alam
(Member)

Hafandi Ahmad, PhD
Senior Lecturer
Faculty of Veterinary Medicine
Universiti Putra Malaysia
(Member)

____
ROBIAH BINTI YUNUS, PhD
Professor and Dean
School of Graduate Studies
Universiti Putra Malaysia

Date:

Declaration by graduate student

I hereby confirm that:

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

Signature: ________________________ Date: ___________________

Name and Matric No.: Nurdiana binti Samsulrizal, (GS41563)

Declaration by Members of Supervisory Committee

This is to confirm that:

- the research conducted and the writing of this thesis was under our supervision;
- supervision responsibilities as stated in the Universiti Putra Malaysia (Graduate Studies) Rules 2003 (Revision 2012-2013) are adhered to.

Signature: ______________________________
Name of Chairman of Supervisory Committee: Associate Professor Dr. Goh Yong Meng

Signature: ______________________________
Name of Member of Supervisory Committee: Associate Professor Dr. Sulaiman Md Dom

Signature: ______________________________
Name of Member of Supervisory Committee: Dr. Hafandi Ahmad

TABLE OF CONTENTS

		Page
ABSTRACT		i
ABSTRAK		iii
ACKNOWLEDGEMENTS		v
APPROVAL		vi
DECLARATION		viii
LIST OF TABLES		xiv
LIST OF FIGURES		xvi
LIST OF ABBREVIATIONS		xix
CHAPTER		
1	**GENERAL INTRODUCTION**	1
	1.1 Context and motivation	1
	1.2 Statement of the problem	1
	1.3 Objectives of the Study	2
	1.4 Significance of the Study	3
	1.5 Structure and outline of the thesis	3
2	**LITERATURE REVIEW**	5
	2.1 Glucose homeostatic mechanisms	5
	2.2 Pancreas	6
	2.3 Brain	7
	2.4 Kidney	8
	2.5 Bone	9
	2.6 Classification of diabetes mellitus	12
	2.7 Mechanisms of hyperglycaemia-induced tissue damage	12
	2.7.1 The diversion of glycolytic flux	13
	2.7.2 Oxidative stress, inflammation and apoptosis	14
	2.8 Tissue oxidative damage related to hyperglycaemia	16
	2.9 Treatment of diabetes mellitus	17
	2.10 *Ficus deltoidea*	20
	2.10.1 Botanical description	20
	2.10.2 Ethnobotanical uses	21
	2.10.3 Chemical composition	22
	2.10.4 Vitexin	23
	2.10.5 Pharmacological properties	24
	2.11 Streptozotocin-based model of diabetic complications	26
	2.11.1 Pancreas	28
	2.11.2 Brain	28
	2.11.3 Kidney	29
	2.11.4 Bone	29
	2.12 Fatty acids as a potential biomarkers for diagnosis purposes	29

2.13 FT-IR spectroscopy 31

3 GENERAL MATERIAL AND METHODS 33
3.1 Plant materials and extract preparations 33
3.2 Animals 33
3.3 Experimental design and procedure 34
3.4 Preparation of tissue homogenates for biochemical assays and FT-IR analysis 36
3.5 Estimation of malondialdehyde (MDA) levels 36
3.6 Assessment of antioxidant enzymatic activities 36
3.7 Fatty acid analysis 36
3.8 FT-IR analysis 37

4 EXPERIMENT I: EFFECTS OF *F. deltoidea* AND VITEXIN TREATMENT ON PANCREATIC HISTOLOGY, INSULIN SECRETION AND OXIDATIVE STATUS IN STZ-INDUCED DIABETIC RATS 38
4.1 Introduction 38
4.1.1 Objective 39
4.2 Materials and Methods 39
4.2.1 Measurement of fasting blood glucose (FBG) 39
4.2.2 Glucose and insulin tolerance measurements 39
4.2.3 Fasting serum insulin 39
4.2.4 Determination of insulin sensitivity 40
4.2.5 Histological assessment 40
4.2.6 Estimation of MDA levels and antioxidant enzymatic activities 41
4.2.7 Fasting amylin 41
4.2.8 Serum and pancreas fatty acid analysis 41
4.2.9 FT-IR analysis for serum and pancreas 41
4.2.10 Statistical analysis 42
4.3 Results 42
4.3.1 Fasting blood glucose 42
4.3.2 Glucose and insulin tolerance 44
4.3.3 Insulin sensitivity 46
4.3.4 Pancreas histology 48
4.3.5 Oxidative stress markers and antioxidant enzymes in the pancreas 50
4.3.6 Amylin levels 51
4.3.7 Serum fatty acid profiles 51
4.3.8 Fatty acid profiles of the pancreas 53
4.3.9 FT-IR spectra of the serum 55
4.3.10 FT-IR spectra of the pancreas 57
4.4 Discussion 62
4.5 Conclusion 65

5 **EXPERIMENT II: EFFECT OF *F. deltoidea* AND VITEXIN ON SPATIAL LEARNING AND MEMORY, CORTICAL GYRIFICATION PATTERNS AND BRAIN OXIDATIVE STRESS MARKERS IN STZ-INDUCED DIABETIC RATS** 66
5.1 Introduction 66
5.1.1 Objective 67
5.2 Materials and Methods 67
5.2.1 Morris Water Maze test (MWM) 67
5.2.2 *vivo* micro-CT analysis of brain 68
5.2.3 Measurement of brain MDA and antioxidant enzymes 68
5.2.4 Estimations of brain insulin and amylin levels 69
5.2.5 Brain fatty acid analysis 69
5.2.6 FT-IR analysis brain 69
5.2.7 Statistical analysis 69
5.3 Results 69
5.3.1 Morris water maze test 69
5.3.2 Micro-computed tomography images of brain 71
5.3.3 Oxidative stress marker and antioxidant enzymes in the brain 73
5.3.4 Changes in the brain insulin and amylin 73
5.3.5 Brain fatty acid changes 74
5.3.6 FT-IR spectra of the brain 76
5.4 Discussion 80
5.5 Conclusion 86

6 **EXPERIMENT III: EFFECT of *F. deltoidea* AND VITEXIN ON RENAL STRUCTURE, FUNCTION AND OXIDATIVE STRESS IN STZ-INDUCED DIABETIC RATS** 87
6.1 Introduction 87
6.1.1 Objective 88
6.2 Materials and Methods 88
6.2.1 Determination of spot urine creatinine 88
6.2.2 Glomerular filtration rate 88
6.2.3 Histological assessment 88
6.2.4 Measurement of renal and liver functional markers 89
6.2.5 Estimation of MDA levels and antioxidant enzymatic activities 89
6.2.6 Analysis of kidney fatty acid composition 89
6.2.7 FT-IR analysis for kidney 89
6.2.8 Statistical analysis 89
6.3 Results 89
6.3.1 Glomerular filtration rate (GFR) 89
6.3.2 Kidney histology 90
6.3.3 The activities of renal and liver function markers 92
6.3.4 Oxidative stress and antioxidant enzyme changes in the renal 94
6.3.5 Renal fatty acid changes 94

6.3.6 FT-IR spectra of the kidney 96
6.3.7 FT-IR spectra of the urine 99
6.4 Discussion 101
6.5 Conclusion 105

7 EXPERIMENT IV: EFFECT OF *F. deltoidea* AND VITEXIN ON BONE HISTOMORPHOMETRIC PARAMETERS, OXIDATIVE STRESS AND BONE TURNOVER MARKERS IN STZ-INDUCED DIABETIC RATS 106
7.1 Introduction 106
7.1.1 Objective 107
7.2 Materials and Methods 107
7.2.1 *Ex vivo* micro-CT analysis of bone 107
7.2.2 Histological assessment 108
7.2.3 Measurement of bone MDA and antioxidant enzymes 108
7.2.4 Marker of bone formation and bone resorption 108
7.2.5 Serum electrolytes 109
7.2.6 Analysis of bone fatty acid composition 109
7.2.7 Statistical analysis 109
7.3 Results 109
7.3.1 Trabecular morphometric parameters 109
7.3.2 Micro computed tomography images of bone 110
7.3.3 Bone histology 112
7.3.4 Oxidative stress marker and antioxidant enzymes in bone 117
7.3.5 Bone turnover markers 117
7.3.6 Changes in serum electrolytes 118
7.3.7 Bone fatty acid changes 119
7.4 Discussion 121
7.5 Conclusion 125

8 GENERAL DISCUSSION 126

9 GENERAL CONCLUSIONS 132
9.1 Recommendations and Future Research 132

REFERENCES 134
APPENDICES 197
BIODATA OF STUDENT 200
LIST OF PUBLICATIONS 201

LIST OF TABLES

Table		Page
4.1	Effect of *F. deltoidea* and vitexin on fasting blood glucose level (mmol/L) in STZ-induced diabetic rats	43
4.2	Effect of *F. deltoidea* and vitexin on serum insulin, HOMA-IR, QUICKI and McAuley index in STZ-induced diabetic rats	47
4.3	Oxidative stress marker and antioxidant enzymes of various experimental groups	50
4.4	Serum fatty acid composition (percentage of total identified fatty acids) of the experimental groups[1]	52
4.5	Fatty acid composition (percentage of total identified fatty acids) of the pancreas of the experimental groups	54
5.1	Depiction of different starting positions in each trail	68
5.2	Probe trial results across treatment groups	71
5.3	Oxidative stress marker and antioxidant enzymes of different experimental groups	73
5.4	Brain insulin and amylin concentrations across experimental groups	73
5.5	Fatty acid composition (percentage of total identified fatty acids) of the brain of the experimental groups[1]	75
6.1	Changes of renal and liver function markers across experimental groups	93
6.2	Changes in oxidative stress and antioxidant enzyme across experimental groups	94
6.3	Fatty acid composition (percentage of total identified fatty acids) of the kidney of the experimental groups[1]	95
7.1	Histomorphometric results obtained on 2D histological sections	110
7.2	Oxidative stress marker and antioxidant enzymes of various experimental groups	117

7.3 Changes in serum osteocalcin, BALP and DPD of various experimental groups 118

7.4 Changes in serum electrolytes of various experimental groups 118

7.5 Fatty acid composition (percentage of total identified fatty acids) of the bone of the experimental groups[1] 120

LIST OF FIGURES

Figure		Page
2.1	Anatomical organization of the pancreas	6
2.2	Schematic diagrams depicting the reciprocal relationships between pancreas, brain, kidney and bone for retaining normal blood glucose levels	11
2.3	A potential mechanism of hyperglycaemia-induced tissue damage	15
2.4	Photograph showing morphological characters of *F. deltoidea*	20
2.5	Photograph showing the morphological differences among the varieties of *F. deltoidea*	21
2.6	Chemical structures of vitexin	23
2.7	Chemical structure of (a) streptozotocin (b) glucose and (c) methylnitrosourea	27
2.8	A Venn diagram summarizes the existing research literature and the missing element related to the present study	32
3.1	Summary of experimental design	35
4.1	Peripheral sensitivity to glucose and insulin	45
4.2	Light photomicrographs of pancreatic sections from different experimental groups	49
4.3	Fasting amylin	51
4.4	Average FT-IR absorption spectra of serum in the regions of (a) 4000-400 cm^{-1} (b) 1200-1000 cm^{-1} from different experimental groups	55
4.5	Second derivative spectra from Figure 4.4B for serum in the regions of 1090-1010 cm^{-1}	56
4.6	Average FT-IR absorption spectra of pancreas in the regions of (a) 4000-400 cm^{-1} (b) 3000-2800 cm^{-1} and (c) 1500-1050 cm^{-1} from different experimental groups	58

4.7 Second derivative spectra from Figure 4.6B for pancreas tissue in the regions of 3000-2800 cm^{-1} 59

4.8 Second derivative spectra from Figure 4.6C for pancreas tissue in the regions of 1440-1380 cm^{-1} 60

4.9 Second derivative spectra from Figure 4.6C for pancreas tissue in the regions of 1190-1000 cm^{-1} 61

5.1 Effects of eight weeks daily of administration of *F. deltoidea* and vitexin on (A) escape latency, (B) mean path length, (C) swimming speed in control and treated diabetic rats, respectively (n=6, mean ± 1 SD) 70

5.2 Cross-sectional micro-CT images of rat brain in 2D 72

5.3 Average FT-IR spectra of brain in the regions of (a) 4000-400 cm^{-1} (b) 3000-2800 cm^{-1} and (c) 1500-1050 cm^{-1} from different experimental groups 77

5.4 Second derivative spectra from Figure 5.3B for brain tissue in the regions of 3000-2800 cm^{-1} 78

5.5 Second derivative spectra from Figure 5.3C for brain tissue in the regions of 1450-1390 cm^{-1} 79

5.6 Second derivative spectra from Figure 5.3C for brain tissue in the regions of 1180-1110 cm^{-1} 80

6.1 Effect of the *F. deltoidea* and vitexin on GFR 90

6.2 Light photomicrographs of glomeruli and renal tubules in the kidney of rats from different experimental groups 91

6.3 Average FT-IR absorption spectra of kidney tissue in the regions of (a) 4000-400 cm^{-1} (b) 1500-1050 cm^{-1} from different experimental groups 97

6.4 Second derivative spectra from Figure 6.3B for kidney tissue in the regions of 1450-1400 cm^{-1} 98

6.5 Second derivative spectra from Figure 6.3B for kidney tissue in the regions of 1180-1110 cm^{-1} 99

6.6 Average FT-IR absorption spectra of urine in the regions of (a) 4000-400 cm^{-1} (b) 1200-950 cm^{-1} from different experimental groups 100

6.7 Second derivative spectra from Figure 6.6B for urine in the regions of 1090-1020 cm^{-1} 101

7.1 Micro-CT images of rat femurs in 2D 111

7.2 Light photomicrographs of distal metaphysis trabecular of rat femur from different experimental groups 113

7.3 Light photomicrographs of distal epiphyseal plate of rat femur from different experimental groups 114

7.4 Light photomicrographs of articular cartilage of rat femur from different experimental groups 115

7.5 Light photomicrographs of cortical bone of femur diaphysis from different experimental groups 116

8.1 The interplay of the pancreas with the brain and bone, as well as kidney that had probably influenced the secretion of insulin 131

LIST OF ABBREVIATIONS

AGEs	advanced glycation end products
ANOVA	analysis of variance
AR	aldose reductase
ATP	adenosine triphosphate
AUC	area under curve
Aβ	β-amyloid
BALP	bone-specific alkaline phosphatase
BF_3	boron trifluoride
BMD	bone mineral density
BV/TV	bone volume ratio
Ca	calcium
cAMP	cyclic adenosine monophosphate
Cl	chloride
°C	degree Celsius
°C/min	degree Celsius per minute
DHA	docosahexaenoic acid
DNA	deoxyribonucleic acid
DPD	deoxypyridinoline
EDTA	ethylenediaminetetraacetic acid
ELISA	enzyme-linked immunosorbent assay
FAME	fatty acid methyl esters
FT-IR	Fourier transform infrared
GAPDH	glyceraldehyde-3-phosphate dehydrogenase
GC	gas chromatography
GFAT	glutamine: fructose-6-phosphate aminotransferase
GFR	Glomerular filtration rate
GK	glucokinase
GLUT2	glucose transporters 2
GPx	glutathione peroxidase
GR	glutathione reductase
H&E	hematoxylin and eosin
H_2O_2	hydrogen peroxide
HBP	hexosamine biosynthetic pathway
HCA	hierarchical cluster analysis
HOMA	homeostatic model assessment
HPLCMS	High-performance liquid chromatography-mass spectrometry
HRP	horseradish peroxidase
HU	Hounsfield units

ICV	intracerebroventricular
IPGTT	intraperitoneal glucose tolerance test
IPITT	intraperitoneal insulin tolerance test
K	potassium
K_2HPO_4	dipotassium hydrogen phosphate trihydrate
KCl	potassium chloride
KOH	potassium hydroxide
MDA	malondialdehyde
micro-CT	micro-computed tomography
mid-IR	mid-infrared
mmol/L	millimoles per litre
MUFA	monounsaturated fatty acid
MWM	Morris Water Maze test
Na	sodium
NADH	nicotinamide adenine dinucleotide
NADPH	nicotinamide adenine dinucleotide phosphate
ng/mL	nanogram per milliliter
nmol/mg	nanomoles per milligrams
$Ocn^{-/-}$	osteocalcin knockout
P	phosphorus
PKC	protein kinase C
PPARγ	peroxisome proliferator-activated receptor gamma
PUFA	polyunsaturated fatty acids
QTOF-LCMS	Quadrupole time of flight liquid chromatography mass spectrometry
QUICKI	quantitative insulin sensitivity check index
ROI	region of interest
ROS	reactive oxygen species
SD	standard deviation
SDH	sorbitol dehydrogenase
SFA	saturated fatty acid
SOD	superoxide dismutase
STZ	Streptozotocin
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
TBARS	thiobarbituric acid reactive substances
TbN	trabecular number
TbSp	trabecular separation
TMB	trimethoxybenzoate
Tris-HCl	tris hydrochloride
U/mg	units per milligrams

CHAPTER 1

GENERAL INTRODUCTION

1.1 Context and motivation

Diabetes mellitus is characterized by hyperglycaemia due to the inability of the body to autonomously regulate the blood glucose levels (Brereton *et al*., 2014). It currently affects about 422 million people worldwide (World Health Organization, 2016), out of which 3.3 million of them have been diagnosed in Malaysia (Hussein *et al*., 2015). Notable in the latter report, diabetes causes 1.5 million deaths in 2012 which derives primarily from complications of persistent hyperglycaemia (Krug, 2016). Pinhas-Hamiel and Zeitler (2005) pointed out that diabetes becomes more common in young adults, adolescents and occasionally, in children. In fact, hyperglycaemia is even postulated as contributing factor for cancer progression (Ryu *et al*., 2014; Lee *et al*., 2016). Despite optimal treatment regimens with insulin or oral diabetes medications, glucose fluctuation in a person with diabetes remains a major challenge (Aronoff *et al*., 2004). These observations suggest that diabetes complications can be overcome, at least, by restoring glucose homeostasis. Therefore, the effective therapeutic strategy in restoring glucose homeostasis requires further investigation.

It is worth noting that acute glucose fluctuations are responsible to influence the magnitude of oxidative stress (Monnier *et al*., 2006; Wu *et al*., 2016). Hyperglycaemia-induced oxidative stress has been postulated as a possible mechanism for diabetes-associated tissue and other systemic complications (Giacco and Brownlee, 2010; Asmat *et al*., 2016). Indeed, a myriad of diabetic tissue damage reported in animal and human studies are driven by oxidative stress regardless of the type of diabetes (Saito *et al*., 2014; Li *et al*., 2015). What is more, these changes are sustained even after hyperglycaemia control is therapeutically achieved (Intine and Sarras, 2012). This is supported by the fact that majority of diabetes treatment expenditures were spent treating diabetes-related complications (Barquera *et al*., 2013). Novel approaches for reversing hyperglycaemic memory and tissue damage, in particular glucose regulation complex are therefore urgently needed.

1.2 Statement of the problem

Over the last few years, glucose regulation has been referred to as a multiorgan process (DeFronzo *et al*., 2012). There are evidences that show the pancreas, brain, kidney and bone play critical roles in orchestrating the control of glucose (Marty *et al*., 2007; Gerich, 2010; Faienza *et al*., 2015). The relationship between blood glucose control, multiplicity of hormonal and neuronal signals by these organs has also been reported in numerous studies (Wei *et al*., 2014; Clemens and Karsenty, 2011). From another perspective, it is well established that dysregulation of glucose homeostasis aggravate oxidative damage by augmenting reactive oxygen species (ROS) production. Pathological changes in the pancreas, brain, kidney and bone are indeed more common in those with diabetes. Despite these observations, the potential link between tissue regeneration and glucose-lowering action is rarely discussed.

Replenishing endogenous insulin, buffering the generation of ROS and optimizing the oxidant-antioxidant balance has recently been identified as the most promising strategies for ameliorating diabetes-induced tissue damage (Kashihara *et al*., 2010; Pimson *et al*., 2014). Although exogenous insulin and oral diabetes medications offer regenerative effect on certain tissue (Marycz *et al*., 2016), the risks appear to outweigh the development of metabolic syndrome and complications. This is mainly due to the difficulties in managing blood glucose fluctuations. In fact, insulin treatment also seems ineffective in the restoration of biomechanical deterioration of bone (Erdal *et al*., 2012).

The past decade has witnessed an increasing interest in exploring medicines derived from plants. Both experimental and clinical studies suggest that the plant based drug is inherently safer and less toxic than pharmaceuticals (Katiyar *et al*., 2012). In fact, multiple evidence strands suggest that the plant extract exerts tissue protective effects (Ezejiofor *et al*., 2013; Wang and Huang, 2014). *F. deltoidea* has been reported to have a glucose-lowering effect and exhibit antioxidant activity (Adam *et al*., 2010; Bhardwaj *et al*., 2015). Similar findings were also noticed in other study related to vitexin, the compound marker of *F. deltoidea* (Choo *et al*., 2012). However, less firm evidence comes from data to explain the role of *F. deltoidea* and vitexin in delaying progression of diabetic tissue damage, particularly on pancreas, brain, kidney and bone.

1.3 Objectives of the Study

The work presented in this thesis investigates the changes in the pancreas, brain, kidney and bone as an integrated functional unit following *F. deltoidea* and vitexin treatment with the purpose of describing the relationships between reversing tissue injury and glucose-lowering action. It was hypothesized that tissue regeneration could be the transmissible element in the lowering of blood glucose and these changes can be determined from the FT-IR spectral. On the basis of these hypotheses, the present study was designed according to the following objectives:

1. To characterize histological and oxidative stress changes in the pancreas of STZ-induced diabetic rats following *F. deltoidea* and vitexin treatment.
2. To identify the effects of *F. deltoidea* and vitexin treatments on behavioural, gyrification patterns and brain oxidative stress markers in diabetic rats.
3. To investigate renal structural and functional changes occurring in STZ-treated rats after *F. deltoidea* and vitexin supplementation.
4. To determine the effects of *F. deltoidea* and vitexin on bone histomorphometry, biochemical and oxidative stress markers in diabetic rats.

1.4 Significance of the Study

The thesis strives to provide valuable information that maintenance of normal glucose homeostasis requires a complex, highly integrated interaction among the pancreas, brain, kidney, and bones. In this regard, an overview of tissue damages related to hyperglycaemia has been shown to demonstrate the associations between inter-organ functions and glucose-lowering action. Methodologically, the thesis introduces a novelty detection approach adopted by FT-IR spectroscopy for examining metabolic fingerprinting related to tissue changes. The study also provides evidence that the brain can be distinguished from the cranium without contrast enhancement using micro-CT. The availability of a rapid and reagent-free method in detecting biochemical and histological changes associated with diabetes may greatly speed up and simplify the diagnosis process. This could also be useful in the future to improve antidiabetic treatment and develop new selective therapies. Above all, this study justifies the use of *F. deltoidea* leaves extract and vitexin as an alternative therapy in the management of diabetes-associated tissue damage.

1.5 Structure and outline of the thesis

This thesis is arranged into nine different chapters. Chapter 2 briefly describes the role of pancreas, brain, kidney and bone in glucose homeostasis. The latter part of literature review focussed on the pathogenic mechanisms of hyperglycaemia-induced tissue damages. Aspects that are relevant to the project are reviewed in order to provide justification for the work carried out and insights into a new possibility in diabetes care by reprogramming cells to repair damaged tissue. Further, this chapter highlights the advantages of herbal medicine particularly on *F. deltoidea* as desirable therapeutic option for enhancing tissue repair. Current approaches of tissue damage detection are summarized at the end of Chapter 2. Description of the general approach and methodology for this study is given in Chapter 3.

In the framework of hyperglycaemia related to tissue damage, the following chapters were included to explore the pathological changes in STZ-treated rats. Chapter 4 serves to illustrate changes in the pancreas histology, antioxidant enzymes, insulin secretion and serum amylin related to fasting blood glucose. The beneficial effect of *F. deltoidea* and vitexin as a therapeutic agent for the management of diabetes-related brain damage was further investigated in Chapter 5. Chapter 6 designed to explore the effects of *F. deltoidea* and vitexin on renal changes, while Chapter 7 elaborates the effect *F. deltoidea* and vitexin on bone loss occurring in STZ-treated rats.

All changes described in Chapter 4, 5, 6 and 7 were summarized and discussed in Chapter 8. This chapter is meant to emphasize the relationship between inter-organ functions and antidiabetic activity. Finally, Chapter 9 concludes the thesis with some closing remarks. Additionally, the outline of possible further research directions is provided.

REFERENCES

Abbasi, E., Nassiri-Asl, M., Shafeei, M. and Sheikhi, M. (2012). Neuroprotective effects of vitexin, a flavonoid, on pentylenetetrazole-induced seizure in rats. *Chem Biol Drug Des.*, 80(2): 274-8.

Abdollahi, M., Zuki, A. B. Z., Goh, Y. M., Rezaeizadeh, A. and Noordin, M. M. (2010). The effects of *Momordica charantia* on the liver in streptozotocin-induced diabetes in neonatal rats. *African Journal of Biotechnology*, 9(31): 5004-5012.

Abdullah, Z., Hussain, K., Zhari, I., Rasadah, M. A., Mazura, P., Jamaludin, F. and Sahdan, R. (2009). Evaluation of extracts of leaf of three *Ficus deltoidea* varieties for antioxidant activities and secondary metabolites. *Phcog Res.*, 1(4): 216-223.

Abdul-Majeed, S., Mohamed, N. and Soelaiman, I. N. (2012). Effects of tocotrienol and lovastatin combination on osteoblast and osteoclast activity in estrogen-deficient osteoporosis. *Evidence-Based Complementary and Alternative Medicine,* 2012: 960742.

Abunasef, S. K., Amin, H. A. and Abdel-Hamid, G. A. (2014). A histological and immunohistochemical study of beta cells in streptozotocin diabetic rats treated with caffeine. *Folia Histochem Cytobiol.*, 52(1): 42-50.

Abuohashish, H. M., Al-Rejaie, S. S., Al-Hosaini, K. A., Parmar, M. Y. and Ahmed, M. M. (2013). Alleviating effects of morin against experimentally-induced diabetic osteopenia. *Diabetol Metab Syndr.*, 5: 5.

Acar, A., Akil, E., Alp, H., Evliyaoglu, O., Kibrisli, E., Inal, A., Unan, F. and Tasdemir, N. (2012). Oxidative damage is ameliorated by curcumin treatment in brain and sciatic nerve of diabetic rats. *Int J Neurosci.*, 122(7): 367-72.

Acharya, N. K., Levin, E. C., Clifford, P. M., Han, M., Tourtellotte, R., Chamberlain, D., Pollaro, M., Coretti, N. J., Kosciuk, M. C., Nagele, E. P., Demarshall, C., Freeman, T., Shi, Y., Guan, C., Macphee, C. H., Wilensky, R. L. and Nagele, R. G. (2013). Diabetes and hypercholesterolemia increase blood-brain barrier permeability and brain amyloid deposition: beneficial effects of the LpPLA2 inhibitor darapladib. *J Alzheimers Dis.*, 35(1): 179-98.

Adam, Z., Hamid, M., Ismail, A. and Khamis, S. (2009). Effect of *Ficus deltoidea* extracts on hepatic basal and insulin-stimulated glucose uptake. *Journal of Biological Sciences*, 9: 796-803.

Adam, Z., Khamis, S., Ismail, A. and Hamid, M. (2010). Inhibitory properties of *Ficus deltoidea* on α-glucosidase activity. *Research Journal of Medicinal Plant*, 4: 61-75.

Adam, Z., Khamis, S., Ismail, A. and Hamid, M. (2012). *Ficus deltoidea*: a potential alternative medicine for diabetes mellitus. *Evidence-Based Complementary and Alternative Medicine*, 2012: 632763.

Adisakwattana, S., Sompong, W., Meeprom, A., Ngamukote, S. and Yibchok-Anun, S. (2012). Cinnamic acid and its derivatives inhibit fructose-mediated protein glycation. *Int J Mol Sci*., 13(2): 1778-89.

Agranoff, B. W., Benjamins, J. A. and Hajra, A. K. (1999). Properties of Brain Lipids. In: Siegel, G. J., Agranoff, B. W. and Albers, R. W. editors. *Basic Neurochemistry: Molecular, Cellular and Medical Aspects*. 6th edition. Philadelphia: Lippincott-Raven.

Ahn, M. Y., Seo, Y. J., Ji, S. D., Han, J. W., Hwang, J. S. and Yun, E. Y. (2010). Fatty acid composition of adipose tissues in obese mice and sd rats fed with Isaria sinclairii powder. *Toxicol Res*., 26(3): 185-92.

Akintunde, J. K. and Oboh, G. (2016). Nephritic cell damage and antioxidant status in rats exposed to leachate from battery recycling industry. *Interdiscip Toxicol*., 9(1): 1-11.

Akkasa, S. B., Severcanb, M., Yilmazc, O. and Severcana, F. (2007). Effects of lipoic acid supplementation on rat brain tissue: an FTIR spectroscopic and neural network study. *Food Chemistry*, 105(3): 1281-1288.

Al-Amin, Z. M., Thomson, M., Al-Qattan, K. K., Peltonen-Shalaby, R. and Ali, M. (2006). Anti-diabetic and hypolipidaemic properties of ginger (*Zingiber officinale*) in streptozotocin-induced diabetic rats. *Br J Nutr*., 96(4): 660-6.

Alhaider, A. A., Korashy, H. M., Sayed-Ahmed, M. M., Mobark, M., Kfoury, H. and Mansour, M. A. (2011). Metformin attenuates streptozotocin-induced diabetic nephropathy in rats through modulation of oxidative stress genes expression. *Chem Biol Interact*., 192(3): 233-42.

Alhazmi, A., Stojanovski, E., Garg, M. L. and McEvoy, M. (2014). Fasting whole blood fatty acid profile and risk of type 2 diabetes in adults: a nested case control study. *PLoS One*, 9(5): e97001.

Al-Qattan, K. K., Thomson, M., Ali, M. and Mansour, M. H. (2013). Garlic (*Allium sativum*) attenuate glomerular glycation in streptozotocin-induced diabetic rats: a possible role of insulin. *Pathophysiology*, 20(2): 147-52.

Alunni, A. and Bally-Cuif, L. (2016). A comparative view of regenerative neurogenesis in vertebrates. *Development*, 143(5): 741-53.

Alzoubi, K. H., Khabour, O. F., Al-Azzam, S. I., Tashtoush, M. H. and Mhaidat, N. M. (2014). Metformin eased cognitive impairment induced by chronic L-methionine administration: potential role of oxidative stress. *Curr Neuropharmacol*., 12(2): 186-92.

American Diabetes Association. (2009). Diagnosis and classification of diabetes mellitus. *Diabetes Care*, 32: S62-S67.

Ami, D., Posteri, R., Mereghetti, P., Porro, D., Doglia, S. M. and Branduardi, P. (2014). Fourier transform infrared spectroscopy as a method to study lipid accumulation in oleaginous yeasts. *Biotechnol Biofuels*, 7(1): 12.

Amin, A., Lotfy, M., Mahmoud-Ghoneim, D., Adeghate, E., Al-Akhras, M. A., Al-Saadi, M., Al-Rahmoun, S. and Hameed, R. (2014). Pancreas-protective effects of chlorella in STZ-induced diabetic animal model: insights into the mechanism *Journal of Diabetes Mellitus*, 1: 36-45.

An, F., Yang, G., Tian, J. and Wang, S. (2012). Antioxidant effects of the orientin and vitexin in *Trollius chinensis* Bunge in D-galactose-aged mice. *Neural Regen Res*., 7(33): 2565-2575.

Anderson, R. A., Zhan, Z., Luo, R., Guo, X., Guo, Q., Zhou, J., Kong, J., Davis, P. A. and Stoecker, B. J. (2015). Cinnamon extract lowers glucose, insulin and cholesterol in people with elevated serum glucose. *J Tradit Complement Med*., 6(4): 332-336.

Andrésdóttir, G., Jensen, M. L., Carstensen, B., Parving, H. H., Hovind, P., Hansen, T. W. and Rossing, P. (2015). Improved prognosis of diabetic nephropathy in type 1 diabetes. *Kidney Int*., 87(2): 417-26.

Anwer, T., Sharma, M., Pillai, K. K. and Khan, G. (2012). Protective effect of *Withania somnifera* against oxidative stress and pancreatic beta-cell damage in type 2 diabetic rats. *Acta Pol Pharm*., 69(6): 1095-101.

Araki, K., Yagi, N., Ikemoto, Y., Yagi, H., Choong, C. J., Hayakawa, H., Beck, G., Sumi, H., Fujimura, H., Moriwaki, T., Nagai, Y., Goto, Y. and Mochizuki, H. (2015). Synchrotron FTIR micro-spectroscopy for structural analysis of Lewy bodies in the brain of Parkinson’s disease patients. *Scientific Reports*, 5: 7625.

Arendt, B. M., Comelli, E. M., Ma, D. W., Lou, W., Teterina, A., Kim, T., Fung, S. K., Wong, D. K., McGilvray, I., Fischer, S. E. and Allard, J. P. (2015). Altered hepatic gene expression in nonalcoholic fatty liver disease is associated with lower hepatic n-3 and n-6 polyunsaturated fatty acids. *Hepatology*, 61(5): 1565-78.

Arikawe, A. P., Udenze, I. C., Akinwolere, M. F., Ogunsola, A. O. and Oghogholosu, R. T. (2012). Effects of streptozotocin, fructose and sucrose-induced insulin resistance on plasma and urinary electrolytes in male Sprague-Dawley rats. *Nig Q J Hosp Med.*, 22(4): 224-30.

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.

Artunc, F., Schleicher, E., Weigert, C., Fritsche, A., Stefan, N. and Häring, H. U. (2016). The impact of insulin resistance on the kidney and vasculature. *Nat Rev Nephrol.*, 12(12): 721-737.

Asada, N., Sato, M. and Katayamaa, Y. (2015). Communication of bone cells with hematopoiesis, immunity and energy metabolism. *Bonekey Rep.*, 4: 748.

Asci, H., Saygin, M., Cankara, F. N., Bayram, D., Yesilot, S., Candan, I. A. and Ilhan, I. (2015). The impact of alpha-lipoic acid on amikacin-induced nephrotoxicity. *Ren Fail.*, 37(1): 117-21.

Ashtarinezhad, A., Panahyab, A., Mohamadzadehasl, B., Vatanpour, H. and Shirazi, F. H. (2015). FT-IR microspectroscopy reveals chemical changes in mice fetus following phenobarbital administration. *Iran J Pharm Res.*, 14: 121-30.

Ashton, J. R., West, J. L. and Badea, C. T. (2015). *In vivo* small animal micro-CT using nanoparticle contrast agents. *Front Pharmacol.*, 6: 256..

Aslam, M. and Sial, A. A. (2014). Neuroprotective effect of ethanol extract of leaves of *Malva parviflora* against amyloid-β- (Aβ-) mediated Alzheimer's disease. *Int Sch Res Notices*, 2014: 156976.

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

Assmann, A., Ueki, K., Winnay, J. N., Kadowaki, T. and Kulkarni, R. N. (2009). Glucose effects on beta-cell growth and survival require activation of insulin receptors and insulin receptor substrate 2. *Mol Cell Biol.*, 29(11): 3219-28.

Atanasov, A. G., Waltenberger, B., Pferschy-Wenzig, E. M., Linder, T., Wawrosch, C., Uhrin, P., Temml, V., Wang, L., Schwaiger, S., Heiss, E. H., Rollinger, J. M., Schuster, D., Breuss, J. M., Bochkov, V., Mihovilovic, M. D., Kopp, B., Bauer, R., Dirsch, V. M. and Stuppner, H. (2015). Discovery and resupply of pharmacologically active plant-derived natural products: a review. *Biotechnol Adv.*, 33(8): 1582-614.

Ayala, A., Muñoz, M. F. and Argüelles, S. (2014). Lipid peroxidation: production, metabolism, and signaling mechanisms of malondialdehyde and 4-hydroxy-2-nonenal. *Oxid Med Cell Longev*., 2014: 360438.

Bačová, B., Seč, P., Certik, M. and Tribulova, N. (2013). Intake of n-3 polyunsaturated fatty acids increases omega-3 index in aged male and female spontaneously hypertensive rats. *ISRN Nutr*., 2013: 209360.

Bahramikia, S. and Yazdanparast, R. (2013). Inhibition of human islet amyloid polypeptide or amylin aggregation by two manganese-salen derivatives. *Eur J Pharmacol*., 707(1-3): 17-25.

Baker, M. J., Trevisan, J., Bassan, P., Bhargava, R., Butler, H. J., Dorling, K. M., Fielden, P. R., Fogarty, S. W., Fullwood, N. J., Heys, K. A., Hughes, C., Lasch, P., Martin-Hirsch, P. L., Obinaju, B., Sockalingum, G. D., Sulé-Suso, J., Strong, R. J., Walsh, M. J., Wood, B. R., Gardner, P. and Martin, F. L. (2014). Using Fourier Transform IR spectroscopy to analyze biological materials. *Nature Protocols*, 9: 1771-1791.

Banerjee, S., Pal, M., Chakrabarty, J., Petibois, C., Paul, R. R., Giri, A. and Chatterjee J. (2015). Fourier-transform-infrared-spectroscopy based spectral-biomarker selection towards optimum diagnostic differentiation of oral leukoplakia and cancer. *Anal Bioanal Chem*., 407(26): 7935-43.

Banki, E., Kovacs, K., Nagy, D., Juhasz, T., Degrell, P., Csanaky, K., Kiss, P., Jancso, G., Toth, G., Tamas, A. and Reglodi, D. (2014). Molecular mechanisms underlying the nephroprotective effects of PACAP in diabetes. *J Mol Neurosci*., 54(3): 300-9.

Barquera, S., Campos-Nonato, I., Aguilar-Salinas, C., Lopez-Ridaura, R., Arredondo, A. and Rivera-Dommarco, J. (2013). Diabetes in Mexico: cost and management of diabetes and its complications and challenges for health policy. *Global Health*, 9: 3.

Basile, K. J., Johnson, M. E., Xia, Q. and Grant, S. F. A. (2014). Genetic susceptibility to type 2 diabetes and obesity: follow-up of findings from genome-wide association studies. *International Journal of Endocrinology*, 2014: 769671.

Baskin, D. G., Stein, L. J., Ikeda, H., Woods, S. C., Figlewicz, D. P., Porte, D. Jr., Greenwood, M. R. and Dorsa, D. M. (1985). Genetically obese Zucker rats have abnormally low brain insulin content. *Life Sci*., 36(7): 627-33.

Bayeva, M., Sawicki, K. T. and Ardehali, H. (2013). Taking diabetes to heart-deregulation of myocardial lipid metabolism in diabetic cardiomyopathy. *J Am Heart Assoc*., 2(6): e000433.

Bazinet, R. P. and Layé, S. (2014). Polyunsaturated fatty acids and their metabolites in brain function and disease. *Nature Reviews Neuroscience*, 15: 771-785.

Bellenger, J., Bellenger, S., Bataille, A., Massey, K. A., Nicolaou, A., Rialland, M., Tessier, C., Kang, J. X. and Narce, M. (2011). High pancreatic n-3 fatty acids prevent STZ-induced diabetes in fat-1 mice: inflammatory pathway inhibition. *Diabetes*, 60(4): 1090-9.

Berenbaum, F. (2011). Diabetes-induced osteoarthritis: from a new paradigm to a new phenotype. *Ann Rheum Dis*., 70(8): 1354-6.

Bergman, H. and Drury, D. R. (1938). The relationship of kidney function to the glucose utilization of the extra abdominal tissues. *Am J Physiol*., 124: 279-284.

Bhardwaj, M., Paul, S., Jakhar, R. and Kang, S. C. (2015). Potential role of vitexin in alleviating heat stress-induced cytotoxicity: regulatory effect of Hsp90 on ER stress-mediated autophagy. *Life Sci*., 142: 36-48.

Bhat, M., Kothiwale, S. K., Tirmale, A. R., Bhargava, S. Y. and Joshi, B. N. (2011). Antidiabetic properties of *Azardiracta indica* and *Bougainvillea spectabilis*: *in vivo* studies in murine diabetes model. *Evidence-Based Complementary and Alternative Medicine,* 2011: 561625.

Bhatta, A., Sangani, R., Kolhe, R., Toque, H. A., Cain, M., Wong, A., Howie, N., Shinde, R., Elsalanty, M., Yao, L., Chutkan, N., Hunter, M., Caldwell, R. B., Isales, C., Caldwell, R. W. and Fulzele, S. (2016). Deregulation of arginase induces bone complications in high-fat/high-sucrose diet diabetic mouse model. *Mol Cell Endocrinol*., 422: 211-20.

Bîcu, M. L., Bîcu, D., Vladu, M. I., Clenciu, D., Chirila, A. M. C., Vîlvoi, D., Sandu, M., Panduru, N. M., Moţa, E. and Moţa, M. (2015). Insulin resistance markers in type 1 diabetes mellitus. *Romanian Journal of Diabetes Nutrition and Metabolic Diseases*, 22(1): 89-98.

Biessels, G. J. and Gispen, W. H. (2005). The impact of diabetes on cognition: what can be learned from rodent models? *Neurobiol Aging*, 1: 36-41.

Biessels, G. J. and Reijmer, Y. D. (2014). Brain changes underlying cognitive dysfunction in diabetes: what can we learn from MRI? *Diabetes*, 63(7): 2244-52.

Biggar, K. K. and Li, S. S. (2015). Non-histone protein methylation as a regulator of cellular signalling and function. *Nat Rev Mol Cell Biol*., 16(1): 5-17.

Bitel, C. L., Kasinathan, C., Kaswala, R. H., Klein, W. L. and Frederikse, P. H. (2012). Amyloid-β and tau pathology of Alzheimer's disease induced by diabetes in a rabbit animal model. *J Alzheimers Dis*., 32(2): 291-305.

Blom, W. A., Stafleu, A., de Graaf, C., Kok, F. J., Schaafsma, G. and Hendriks, H. F. (2005). Ghrelin response to carbohydrate-enriched breakfast is related to insulin. *Am J Clin Nutr*., 81(2): 367-75.

Blondeau, N., Nguemeni, C., Debruyne, D. N., Piens, M., Wu, X., Pan, H., Hu, X., Gandin, C., Lipsky, R. H., Plumier, J. C., Marini, A. M. and Heurteaux, C. (2009). Subchronic alpha-linolenic acid treatment enhances brain plasticity and exerts an antidepressant effect: a versatile potential therapy for stroke. *Neuropsychopharmacology*, 34(12): 2548-59.

Boesten, D. M. P. H. J., von Ungern-Sternberg, S. N. I., den Hartog, G. J. M. and Bast, A. (2014). Protective pleiotropic effect of flavonoids on NAD^+ levels in endothelial cells exposed to high glucose. *Oxidative Medicine and Cellular Longevity*, 2015: 894597.

Bombalska, A., Mularczyk-Oliwa, M., Kwaśny, M., Włodarski, M., Kaliszewski, M., Kopczyński, K., Szpakowska, M. and Trafny, E. A. (2011). Classification of the biological material with use of FT-IR spectroscopy and statistical analysis. *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy*, 78 (4): 1221-1226.

Bonjour, J. P. (2011). Calcium and phosphate: a duet of ions playing for bone health. *J Am Coll Nutr*., 30: 438S-48S.

Boon, A. C., Lam, A. K., Gopalan, V., Benzie, I. F., Briskey, D., Coombes, J. S., Fassett, R. G. and Bulmer, A. C. (2015). Endogenously elevated bilirubin modulates kidney function and protects from circulating oxidative stress in a rat model of adenine-induced kidney failure. *Scientific Reports*, 5: 15482.

Bortolin, R. H., da Graça Azevedo Abreu, B. J., Abbott Galvão Ururahy, M., Costa de Souza, K. S., Bezerra, J. F., Loureiro, M. B., da Silva, F. S., Marques, D. E., Batista, A. A., Oliveira, G., Luchessi, A. D., Lima, V. M., Miranda, C. E., Lia Fook, M. V., Almeida, Md., de Rezende, L. A. and de Rezende, A. A. (2015). Protection against T1DM-induced bone loss by zinc supplementation: biomechanical, histomorphometric, and molecular analyses in stz-induced diabetic rats. *PLoS One*, 10(5): e0125349.

Boskey, A. and Camacho, N. P. (2007). FT-IR imaging of native and tissue-engineered bone and cartilage. *Biomaterials*, 28(15): 2465-2478.

Braun, U., Ohlerth, S., Liesegang, A., Forster, E., Gorber, U., Tschuor, A., Bearth, G., Muntwyler, J., Wiederkehr, D. and Ossent, P. (2009). Osteoporosis in goats associated with phosphorus and calcium deficiency. *Vet Rec*., 164(7): 211-3.

Brereton, M. F., Iberl, M., Shimomura, K. and Zhang, Q., Adriaenssens, A. E., Proks, P., Spiliotis, I. I., Dace, W., Mattis, K. K., Ramracheya, R., Gribble, F. M., Reimann, F., Clark, A., Rorsman, P. and Ashcroft, F. M. (2014). Reversible changes in pancreatic islet structure and function produced by elevated blood glucose. *Nature Communications*, 5: 4639.

Brereton, M. F., Vergari, E., Zhang, Q. and Clark, A. (2015). Alpha-, delta- and pp-cells: are they the architectural cornerstones of islet structure and co-ordination? *J Histochem Cytochem*., 63(8): 575-91.

Bucris, E., Beck, A., Boura-Halfon, S., Isaac, R., Vinik, Y., Rosenzweig, T., Sampson, S. R. and Zick, Y. (2016). Prolonged insulin treatment sensitizes apoptosis pathways in pancreatic β cells. *J Endocrinol*., 230(3): 291-307.

Bunawan, H., Amin, N. M., Bunawan, S. N., Baharum, S. N. and Mohd Noor, N. (2014). *Ficus deltoidea* Jack: a review on its phytochemical and pharmacological importance. *Evid Based Complement Alternat Med*., 2014: 902734.

Burge, R., Dawson-Hughes, B., Solomon, D. H., Wong, J. B., King, A. and Tosteson, A. (2007). Incidence and economic burden of osteoporosis-related fractures in the United States, 2005-2025. *J Bone Miner Res*., 22(3): 465-75.

Burghardt, A. J., Link, T. M. and Majumdar, S. (2011). High-resolution computed tomography for clinical imaging of bone microarchitecture. *Clin Orthop Relat Res*., 469(8): 2179-93.

Bylda, C., Thiele, R., Kobold, U. and Volme, D. A. (2014). Recent advances in sample preparation techniques to overcome difficulties encountered during quantitative analysis of small molecules from biofluids using LC-MS/MS. *Analyst*, 139: 2265-2276.

Cabrera, O., Berman, D. M., Kenyon, N. S., Ricordi, C., Berggren, P. O. and Caicedo, A. (2006). The unique cytoarchitecture of human pancreatic islets has implications for islet cell function. *Proc Natl Acad Sci U S A*., 103(7): 2334-9.

Cai, K., Qi, D., Wang, O., Chen, J., Liu, X., Deng, B., Qian, L., Liu, X. and Le, Y. (2011). TNF-alpha acutely upregulates amylin expression in murine pancreatic beta cells. *Diabetologia,* 54(3): 617-26.

Cai, X. and McGinnis, J. F. (2016). Diabetic retinopathy: animal models, therapies, and perspectives. *Journal of Diabetes Research*, 2016: 3789217.

Calvo, E., Palacios, I., Delgado, E., Ruiz-Cabello, J., Hernández, P., Sánchez-Pernaute, O., Egido, J. and Herrero-Beaumont, G. (2001). High-resolution

MRI detects cartilage swelling at the early stages of experimental osteoarthritis. *Osteoarthritis Cartilage*, 9(5): 463-72.

Canal, C. E., Stutz, S. J. and Gold, P. E. (2005). Glucose injections into the dorsal hippocampus or dorsolateral striatum of rats prior to T-maze training: modulation of learning rates and strategy selection. *Learn Mem.,* 12(4): 367-374.

Cantley, J. and Ashcroft, F. M. (2015). Q&A: insulin secretion and type 2 diabetes: why do β-cells fail? *BMC Biol*., 13: 33.

Cao, X. H., Zhao, S. S., Liu, D. Y., Wang, Z., Niu, L. L., Hou, L. H. and Wang, C. L. (2011). ROS-Ca($^{2+}$) is associated with mitochondria permeability transition pore involved in surfactin-induced MCF-7 cells apoptosis. *Chem Biol Interact*., 90(1): 16-27.

Carlessi, R., Lemos, N. E., Dias, A. L., Oliveira, F. S., Brondani, L. A., Canani, L. H., Bauer, A. C., Leitão, C. B. and Crispim, D. (2015). Exendin-4 protects rat islets against loss of viability and function induced by brain death. *Mol Cell Endocrinol*., 412: 239-50.

Cator, L. J., Pietri, J. E., Murdock, C. C., Ohm, J. R., Lewis, E. E., Read, A. F., Luckhart, S. and Thomas, M. B. (2015). Immune response and insulin signalling alter mosquito feeding behaviour to enhance malaria transmission potential. *Sci Rep*., 5: 11947.

Cermenati, G., Abbiati, F., Cermenati, S., Brioschi, E., Volonterio, A., Cavaletti, G., Saez, E., De Fabiani, E., Crestani, M., Garcia-Segura, L. M., Melcangi, R. C., Caruso, D. and Mitro, N. (2012). Diabetes-induced myelin abnormalities are associated with an altered lipid pattern: protective effects of LXR activation. *J Lipid Res*., 53(2): 300-10.

Cernea, S. and Dobreanu, M. (2013). Diabetes and beta cell function: from mechanisms to evaluation and clinical implications. *Biochem Med (Zagreb)*., 23(3): 266-80.

Cersosimo, E., Solis-Herrera, C. and Triplitt, C. (2014). Inhibition of renal glucose reabsorption as a novel treatment for diabetes patients. *J Bras Nefrol*., 36(1): 80-92.

Chaudhry, Z. Z., Morris, D. L., Moss, D. R., Sims, E. K., Chiong, Y., Kono, T. and Evans-Molina, C. (2013). Streptozotocin is equally diabetogenic whether administered to fed or fasted mice. *Lab Anim*., 47(4): 257-65.

Chen, C. and Omiya, Y. (2014). Brain asymmetry in cortical thickness is correlated with cognitive function. *Front Hum Neurosci*., 8: 877.

Chen, C., Yu, X. and Shao, S. (2015). Effects of omega-3 fatty acid supplementation on glucose control and lipid levels in type 2 diabetes: a meta-analysis. *PLoS One*, 10(10): e0139565.

Chen, G. C., Yang, J., Eggersdorfer, M., Zhang, W. and Qin, L. Q. (2016). N-3 long-chain polyunsaturated fatty acids and risk of all-cause mortality among general populations: a meta-analysis. *Scientific Reports*, 6: 28165.

Chen, L., LaRocque, L. M., Efe, O., Wang, J., Sands, J. M. and Klein, J. D. (2016). Effect of dapagliflozin treatment on fluid and electrolyte balance in diabetic rats. *The American Journal of the Medical Sciences*, 352(5): 517-523.

Chen, R., Kang, R., Fan, X. G. and Tang, D. (2014). Release and activity of histone in diseases. *Cell Death Dis.*, 5: e1370.

Chen, Y. J., Cheng, Y. D., Liu, H. Y., Lin, P. Y. and Wang, C. S. (2006). Observation of biochemical imaging changes in human pancreatic cancer tissue using Fourier-transform infrared microspectroscopy. *Chang Gung Med J.*, 29(5): 518-27.

Chera, S. and Herrera, P. L. (2016). Regeneration of pancreatic insulin-producing cells by in situ adaptive cell conversion. *Curr Opin Genet Dev.*, 40: 1-10.

Cheung, C. L., Tan, K. C., Lam, K. S. and Cheung, B. M. (2013). The relationship between glucose metabolism, metabolic syndrome, and bone-specific alkaline phosphatase: a structural equation modeling approach. *J Clin Endocrinol Metab.*, 98(9): 3856-63.

Cho, J. H., Kim, J. W., Shin, J. A., Shin, J. and Yoon, K. H. (2011). β-cell mass in people with type 2 diabetes. *J Diabetes Investig.*, 2(1): 6-17.

Choo, C. Y., Sulong, N. Y., Man, F. and Wong, T. W. (2012). Vitexin and isovitexin from the leaves of *Ficus deltoidea* with *in-vivo* α-glucosidase inhibition. *J Ethnopharmacol.*, 142(3): 776-81.

Chorváthová, V. and Ondreicka, R. (1983). The fatty acid composition of the tissues of streptozotocin-diabetic rats. *Physiol Bohemoslov.*, 32(5): 466-75.

Chow, F. Y., Nikolic-Paterson, D. J., Atkins, R. C. and Tesch, G. H. (2004). Macrophages in streptozotocin-induced diabetic nephropathy: potential role in renal fibrosis. *Nephrol Dial Transplant.*, 19(12): 2987-96.

Chugh, S. S., Macé, C., Clement, L. C., Avila, M. D. N. and Marshall, C. B. (2014). Angiopoietin-like 4 based therapeutics for proteinuria and kidney disease. *Front Pharmacol.*, 5: 23.

Ciobanu, D. M., Olar, L. E., Stefan, R., Veresiu, I. A., Bala, C. G., Mircea, P. A. and Roman, G. (2015). Fluorophores advanced glycation end products (AGEs)-to-NADH ratio is predictor for diabetic chronic kidney and cardiovascular disease. *J Diabetes Complications*, 29(7): 893-7.

Clemens, T. L. and Karsenty, G. (2011). The osteoblast: an insulin target cell controlling glucose homeostasis. *J Bone Miner Res*., 26(4): 677-80.

Coll, A. P. and Yeo, G. S. (2013). The hypothalamus and metabolism: integrating signals to control energy and glucose homeostasis. *Curr Opin Pharmacol*., 13(6): 970-6.

Collino, M., Aragno, M., Castiglia, S., Tomasinelli, C., Thiemermann, C., Boccuzzi, G. and Fantozzi, R. (2009). Insulin reduces cerebral ischemia/reperfusion injury in the hippocampus of diabetic rats: a role for glycogen synthase kinase-3beta. *Diabetes*, 58(1): 235-42.

Contreras, J. L., Eckstein, C., Smyth, C. A., Sellers, M. T., Vilatoba, M., Bilbao, G., Rahemtulla, F. G., Young, C. J., Thompson, J. A., Chaudry, I. H. and Eckhoff, D. E. (2003). Brain death significantly reduces isolated pancreatic islet yields and functionality *in vitro* and *in vivo* after transplantation in rats. *Diabetes*, 52(12): 2935-42.

Corner, E. J. H. (1969). The complex of Ficus deltoidea; a recent invasion of the Sunda Shelf. *Philosophical Transactions of the Royal Society of London*, 256: 281-317.

Costa, R., Tamascia, M. L., Nogueira, M. D., Casarini, D. E. and Marcondes, F. K. (2012). Handling of adolescent rats improves learning and memory and decreases anxiety. *J Am Assoc Lab Anim Sci*., 51(5): 548-53.

Covic, A., Gusbeth-Tatomir, P. and Goldsmith, D. (2008). Negative outcome studies in end-stage renal disease: how dark are the storm clouds? *Nephrol Dial Transplant*., 23(1): 56-61.

Cox, D. J., Kovatchev, B. P., Gonder-Frederick, L. A., Summers, K. H., McCall, A., Grimm, K. J. and Clarke, W. L. (2005). Relationships between hyperglycemia and cognitive performance among adults with type 1 and type 2 diabetes. *Diabetes Care*, 28(1): 71-7.

Coyle, C., Cafferty, F. H., Vale, C. and Langley, R. E. (2016). Metformin as an adjuvant treatment for cancer: a systematic review and meta-analysis. *Ann Oncol*., 27(12): 2184-2195.

Creecy, A., Uppuganti, S., Merkel, A. R., O'Neal, D., Makowski, A. J., Granke, M., Voziyan, P. and Nyman, J. S. (2016). Changes in the fracture resistance of bone with the progression of type 2 diabetes in the ZDSD rat. *Calcif Tissue Int*., 99(3): 289-301.

Cui, W., Ma, J., Wang, X., Yang, W., Zhang, J. and Ji, Q. (2013). Free fatty acid induces endoplasmic reticulum stress and apoptosis of β-cells by Ca^{2+}/calpain-2 pathways. *PLoS One*, 8(3): e59921.

Cunnane, S. C., Schneider, J. A., Tangney, C., Tremblay-Mercier, J., Fortier, M., Bennett, D. A. and Morris, M. C. (2012). Plasma and brain fatty acid profiles in mild cognitive impairment and Alzheimer's disease. *J Alzheimers Dis*., 29(3): 691-7.

Cusi, K. and Defronzo, R. A. (1998). Metformin: a review of its metabolic effects. *Diabetes Reviews*, 6: 89-131.

Dai, H., Liu, Q. and Liu, B. (2017). Research progress on mechanism of podocyte depletion in diabetic nephropathy. *Journal of Diabetes Research*, 2017: 2615286.

Davidson, M. B. (2009). Pro's and con's of the early use of insulin in the management of type 2 diabetes: a clinical evaluation. *Curr Opin Endocrinol Diabetes Obes*., 16(2): 107-12.

de Almeida Chaves Rodrigues, A. F., de Lima, I. L., Bergamaschi, C. T., Campos, R. R., Hirata, A. E., Schoorlemmer, G. H. and Gomes, G. N. (2013). Increased renal sympathetic nerve activity leads to hypertension and renal dysfunction in offspring from diabetic mothers. *Am J Physiol Renal Physiol*., 304(2): F189-97.

de Assis, A. M., Rech, A., Longoni, A., da Silva Morrone, M., de Bittencourt Pasquali, M. A., Perry, M. L., Souza, D. O. and Moreira, J. C. (2015). Dietary n-3 polyunsaturated fatty acids revert renal responses induced by a combination of 2 protocols that increase the amounts of advanced glycation end product in rats. *Nutr Res*., 35(6): 512-22.

De Monte, C., Carradori, S., Granese, A., Di Pierro, G. B., Leonardo, C. and De Nunzio C. (2014). Modern extraction techniques and their impact on the pharmacological profile of *Serenoa repens* extracts for the treatment of lower urinary tract symptoms. *BMC Urol*., 14: 63.

DeFronzo, R. A., Davidson, J. A. and Del Prato, S. (2012). The role of the kidneys in glucose homeostasis: a new path towards normalizing glycaemia. *Diabetes Obes Metab*., 14(1): 5-14.

DeFronzo, R. A., Triplitt, C. L., Abdul-Ghani, M. and Cersosimo, E. (2014). Novel agents for the treatment of type 2 diabetes. *Diabetes Spectr*., 27(2): 100-112.

Demaurex, N. and Scorran, L. (2009). Reactive oxygen species are NOXious for neurons. *Nature Neuroscience*, 12: 819-820.

Demir, P., Akkas, S. B., Severcan, M., Zorlu, F. and Severcan, F. (2015). Ionizing radiation induces structural and functional damage on the molecules of rat brain homogenate membranes: a Fourier transform infrared (FT-IR) spectroscopic study. *Appl Spectrosc*., 69(1): 154-64.

Deng, S., Markmann, J. F., Rickels, M., Yeh, H., Kim, J. I., Lian, M. M., Gu, Y., Markmann, E., Palanjian, M., Barker, C. F. and Naji, A. (2009). Islet alone vs. islet after kidney transplantation: metabolic outcomes and islet graft survival. *Transplantation*, 88(6): 820-825.

Deng, Y. T., Kang, W. B., Zhao, J. N., Liu, G. and Zhao, M. G. (2015). Osteoprotective effect of echinocystic acid, a triterpone component from eclipta prostrata, in ovariectomy-induced osteoporotic rats. *PLoS One*., 10(8): e0136572.

Deschepper, M., Oudina, K., David, B., Myrtil, V., Collet, C., Bensidhoum, M., Logeart-Avramoglou, D. and Petite, H. (2011). Survival and function of mesenchymal stem cells (MSCs) depend on glucose to overcome exposure to long-term, severe and continuous hypoxia. *J Cell Mol Med*., 15(7): 1505-14.

Detaille, D., Vial, G., Borel, A. L., Cottet-Rouselle, C., Hallakou-Bozec, S., Bolze, S., Fouqueray, P. and Fontaine, E. (2016). Imeglimin prevents human endothelial cell death by inhibiting mitochondrial permeability transition without inhibiting mitochondrial respiration. *Cell Death Discovery*, 2: 15072.

Dhuria, R. S., Singh, G., Kaur, A., Kaur, R. and Kaur, T. (2015). Current status and patent prospective of animal models in diabetic research. *Adv Biomed Res*., 4: 117.

Di Nunzio, M., Valli, V. and Bordoni, A. (2016). PUFA and oxidative stress. Differential modulation of the cell response by DHA. *Int J Food Sci Nutr*., 67(7): 834-43.

Ding, Y., Zhang, Z., Dai, X., Jiang, Y., Bao, L., Li, Y. and Li, Y. (2013). Grape seed proanthocyanidins ameliorate pancreatic beta-cell dysfunction and death in low-dose streptozotocin- and high-carbohydrate/high-fat diet-induced diabetic rats partially by regulating endoplasmic reticulum stress. *Nutr Metab (Lond)*., 10: 51.

Dolenšek, J., Rupnik, M. S. and Stožer, A. (2015). Structural similarities and differences between the human and the mouse pancreas. *Islets*, 7(1): e1024405.

Domingueti, C. P., Dusse, L. M., Carvalho, M., de Sousa, L. P., Gomes, K. B. and Fernandes, A. P. (2016). Diabetes mellitus: the linkage between oxidative stress, inflammation, hypercoagulability and vascular complications. *J Diabetes Complications*, 30(4): 738-45.

Dong, Y., Jing, T., Meng, Q., Liu, C., Hu, S., Ma, Y., Liu, Y., Lu, J., Cheng, Y., Wang, D. and Teng L. (2014). Studies on the antidiabetic activities of *Cordyceps militaris* extract in diet-streptozotocin-induced diabetic Sprague-dawley rats. *BioMed Research International*, 2014: 160980.

Donga, E., van Dijk, M., Hoogma, R. P., Corssmit, E. P. and Romijn, J. A. (2013). Insulin resistance in multiple tissues in patients with type 1 diabetes mellitus on long-term continuous subcutaneous insulin infusion therapy. *Diabetes Metab Res Rev*., 29(1): 33-8.

Douard, V., Asgerally, A., Sabbagh, Y., Sugiura, S., Shapses, S. A., Casirola, D. and Ferraris, R. P. (2010). Dietary fructose inhibits intestinal calcium absorption and induces vitamin D insufficiency in CKD. *J Am Soc Nephrol*., 21(2): 261-71.

Draman, S., Aris, M. A. M., Akter, S. F. U., Azlina, H., Nor Azlina, A. R. and Norazlanshah, H. (2012). Mas cotek (*Ficus deltoidea*): a possible supplement for type II diabetes: (a pilot study). *Pertanika Journal of Tropical Agricultural Science*, 35: 93-102.

Dreissig, I., Machill, S., Salzer, R. and Krafft, C. (2009). Quantification of brain lipids by FTIR spectroscopy and partial least squares regression. *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy*, 71(5): 2069-2075.

Du, X. L. (2000). Hyperglycemia-induced mitochondrial superoxide overproduction activates the hexosamine pathway and induces plasminogen activator inhibitor-1 expression by increasing Sp1 glycosylation. *PNAS*, 97: 12222-12226.

Dufrane, D., van Steenberghe, M., Guiot, Y., Goebbels, R. M., Saliez, A. and Gianello, P. (2006). Streptozotocin-induced diabetes in large animals (pigs/primates): role of GLUT2 transporter and beta-cell plasticity. *Transplantation*, 81(1): 36-45.

Dzolin, S., Ahmad, R., Zain, M. M. and Ismail, M. I. (2015). Flavonoid distribution in four varieties of *Ficus deltoidea* (Jack). *J Med Plant Herb Ther Res*., 3: 1-9.

Eirin, A., Li, Z., Zhang, X., Krier, J. D., Woollard, J. R., Zhu, X. Y., Tang, H., Herrmann, S. M., Lerman, A., Textor, S. C. and Lerman, L. O. (2012). A mitochondrial permeability transition pore inhibitor improves renal outcomes after revascularization in experimental atherosclerotic renal artery stenosis. *Hypertension*, 60(5): 1242-9.

El Assar, M., Angulo, J., Santos-Ruiz, M., Moreno, P., Novials, A., Villanueva-Peñacarrillo, M. L. and Rodríguez-Mañas, L. (2015). Differential effect of amylin on endothelial-dependent vasodilation in mesenteric arteries from control and insulin resistant rats. *PLoS One*, 10(3): e0120479.

El Karib, A. O., Al-Ani, B., Al-Hashem, F., Dallak, M., Bin-Jaliah, I., El-Gamal, B., Bashir, S. O., Eid, R. A. and Haidara, M. A. (2016). Insulin and vanadium protect against osteoarthritis development secondary to diabetes mellitus in rats. *Arch Physiol Biochem*., 122(3): 148-54.

El-Akabawy, G. and El-Kholy, W. (2014). Neuroprotective effect of ginger in the brain of streptozotocin-induced diabetic rats. *Ann Anat*., 196(2-3): 119-28.

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. *J Diabetes Metab Disord*., 12(1): 60.

Ellegaard, M., Thorkildsen, C., Petersen, S., Petersen, J. S., Jørgensen, N. R., Just, R., Schwarz, P., Ramirez, M. T. and Stahlhut, M. (2010). Amylin(1-8) is devoid of anabolic activity in bone. *Calcif Tissue Int*., 86(3): 249-60.

Emami, A., Ghadiri, H. and Ghafarian, P. (2014). Performance evaluation of bone mineral densitometry techniques by a novel phantom. *Frontier Biomedical Technologies*, 1: 271-278.

Erdal, N., Gürgül, S., Demirel, C. and Yildiz, A. (2012). The effect of insulin therapy on biomechanical deterioration of bone in streptozotocin (STZ)-induced type 1 diabetes mellitus in rats. *Diabetes Res Clin Pract*., 97(3): 461-467.

Erdal, N., Gürgül, S., Kavak, S., Yildiz, A. and Emre, M. (2011). Deterioration of bone quality by streptozotocin (STZ)-induced type 2 diabetes mellitus in rats. *Biol Trace Elem Res*., 140(3): 342-53.

Erion, R. and Sehgal, A. (2013). Regulation of insect behavior via the insulin-signaling pathway. *Front Physiol*., 4: 353.

Eslami, H., Batavani, R. A., Asr I-Rezaei, S. and Hobbenaghi, R. (2015). Changes of stress oxidative enzymes in rat mammary tissue, blood and milk after experimental mastitis induced by *E. coli* lipopolysaccharide. *Vet Res Forum*., 6(2): 131-6.

Espeland, M. A., Bryan, R. N., Goveas, J. S., Robinson, J. G., Siddiqui, M. S., Liu, S., Hogan, P. E., Casanova, R., Coker, L. H., Yaffe, K., Masaki, K., Rossom, R. and Resnick, S. M. (2013). Influence of type 2 diabetes on brain volumes and changes in brain volumes results from the women's health initiative magnetic resonance imaging studies. *Diabetes Care*, 36: 90-97.

Evan, A. P., Mong, S. A., Gattone, V. H., Connors, B. A., Aronoff, G. R. and Luft, F. C. (1984). The effect of streptozotocin and streptozotocin-induced diabetes on the kidney. *Ren Physiol*., 7(2): 78-89.

Ezejiofor, A. N., Okorie, A. and Orisakwe, O. E. (2013). Hypoglycaemic and tissue-protective effects of the aqueous extract of Persea americana seeds on alloxan-induced albino rats. *Malays J Med Sci*., 20(5): 31-39.

Ezquer, F. E., Ezquer, M. E., Parrau, D. B., Carpio, D., Yañez, A. J. and Conget, P. A. (2008). Systemic administration of multipotent mesenchymal stromal cells reverts hyperglycemia and prevents nephropathy in type 1 diabetic mice. *Biol Blood Marrow Transplant*., 14(6): 631-640.

Ezuruike, U. F. and Prieto, J. M. (2014). The use of plants in the traditional management of diabetes in Nigeria: pharmacological and toxicological considerations. *J Ethnopharmacol*., 155(2): 857-924.

Faienza, M. F., Luce, V., Ventura, A., Colaianni, G., Colucci, S., Cavallo, L., Grano, M. and Brunetti, G. (2015). Skeleton and glucose metabolism: a bone-pancreas loop. *Int J Endocrinol*., 2015: 758148.

Farshid, A. A. and Tamaddonfard, E. (2015). Histopathological and behavioral evaluations of the effects of crocin, safranal and insulin on diabetic peripheral neuropathy in rats. *Avicenna J Phytomed*., 5(5): 469-78.

Farsi, E., Ahmad, M., Hor, S. Y., Ahamed, M. B., Yam, M. F. and Asmawi. M. Z. (2014). Standardized extract of *Ficus deltoidea* stimulates insulin secretion and blocks hepatic glucose production by regulating the expression of glucose-metabolic genes in streptozitocin-induced diabetic rats. *BMC Complement Altern Med*.,14: 220.

Farsi, E., Shafaei, A., Hor, S. Y., Ahamed, M. B. K., Yam, M. F., Attitalla, I. H., Asmawi, M. Z. and Ismail, Z. (2011). Correlation between enzymes inhibitory effects and antioxidant activities of standardized fractions of methanolic extract obtained from *Ficus deltoidea* leaves. *African Journal of Biotechnology*, 10: 15184-15194.

Fatihah, H. N., Mat, N., Zaimah, A. R., Zuhailah, M. N., Norhaslinda, H., Khairil, M., Ghani, A. Y. and Ali, A. M. (2012). Morphological phylogenetic analysis of seven varieties of *Ficus deltoidea* Jack from the Malay Peninsula of Malaysia. *PLoS One*, 7(12): e52441.

Feltes, C. M., Van Eyk, J. and Rabb, H. (2008). Distant-organ changes after acute kidney injury. *Nephron Physiol*., 109(4): 80-84.

Feng, X. and McDonald, J. M. (2011). Disorders of bone remodeling. *Annu Rev Pathol*., 6: 121-45.

Ferron, M., Wei, J., Yoshizawa, T., Del Fattore, A., DePinho, R. A., Teti, A., Ducy, P. and Karsenty, G. (2010). Insulin signaling in osteoblasts integrates bone remodeling and energy metabolism. *Cell*, 142(2): 296-308.

Fields, R. D. (2013). Changes in brain structure during learning: fact or artifact? Reply to Thomas and Baker. *Neuroimage*, 73: 260-4.

Flachs, P., Rossmeisl, M. and Kopecky, J. (2014). The effect of n-3 fatty acids on glucose homeostasis and insulin sensitivity. *Physiol Res*., 63: S93-118.

Folch, J., Lees, M. and Sloane Stanley, G. H. (1957). A simple method for the isolation and purification of total lipides from animal tissues. *J Biol Chem*., 226(1): 497-509.

Fonseca, S. G., Burcin, M., Gromada, J. and Urano, F. (2009). Endoplasmic reticulum stress in beta-cells and development of diabetes. *Curr Opin Pharmacol*., 9(6): 763-70.

Forbes, J. M. and Cooper, M. E. (2013). Mechanisms of diabetic complications. *Physiol Rev*., 93(1): 137-88.

Forbes, J. M., Coughlan, M. T. and Cooper, M. E. (2008). Oxidative stress as a major culprit in kidney disease in diabetes. *Diabetes*, 57(6): 1446-54.

Francisqueti, F. V., Santos, K. C., Ferron, A. J., Lo, A. T., Minatel, I. O., Campos, D. H., Ferreira, A. L. and Corrêa, C. R. (2016). Fructose: toxic effect on cardiorenal risk factors and redox state. *SAGE Open Med*., 4: 2050312116684294.

Franko, A., Huypens, P., Neschen, S., Irmler, M., Rozman, J., Rathkolb, B., Neff, F., Prehn, C., Dubois, G., Baumann, M., Massinger, R., Gradinger, D., Przemeck, G. K., Repp, B., Aichler, M., Feuchtinger, A., Schommers, P., Stöhr, O., Sanchez-Lasheras, C., Adamski, J., Peter, A., Prokisch, H., Beckers, J., Walch, A. K., Fuchs, H., Wolf, E., Schubert, M., Wiesner, R. J. and Hrabě de Angelis, M. (2016). Bezafibrate improves insulin sensitivity and metabolic flexibility in stz-induced diabetic mice. *Diabetes,* 65(9): 2540-52.

Freeman, J. S. (2009). Insulin analog therapy: improving the match with physiologic insulin secretion. *J Am Osteopath Assoc*., 109(1): 26-36.

Frings-Meuthen, P., Buehlmeier, J., Baecker, N., Stehle, P., Fimmers, R., May, F., Kluge, G. and Heer, M. (2011). High sodium chloride intake exacerbates immobilization-induced bone resorption and protein losses. *J Appl Physiol (1985).,* 111(2): 537-42.

Fuentes, A. L., Hennessy, K., Pascual, J., Pepe, N., Wang, I., Santiago, A., Chaggan, C., Martinez, J., Rivera, E., Cota, P., Cunha, C., Nogaj, L. A. and Moffet, D. A. (2016). Identification of plant extracts that inhibit the formation of diabetes-linked IAPP amyloid. *J Herb Med*., 6(1): 37-41.

Fukaya, T., Gondaira, T., Kashiyae, Y., Kotani, S., Ishikura, Y., Fujikawa, S., Kiso, Y. and Sakakibara, M. (2007). Arachidonic acid preserves hippocampal neuron membrane fluidity in senescent rats. *Neurobiol Aging*, 28(8): 1179-86.

Fuster-Matanzo, A., Llorens-Martín, M., Hernández, F. and Avila, J. (2013). Role of neuroinflammation in adult neurogenesis and Alzheimer disease: therapeutic approaches. *Mediators Inflamm*., 2013: 260925.

Gajjar, K., Trevisan, J., Owens, G., Keating, P. J., Wood, N. J., Stringfellow, H. F., Martin-Hirsch, P. L. and Martin, F. L. (2013). Fourier-transform infrared spectroscopy coupled with a classification machine for the analysis of blood plasma or serum: a novel diagnostic approach for ovarian cancer. *Analyst*., 138(14): 3917-26.

Ganugula, R., Arora, M., Jaisamut, P., Wiwattanapatapee, R., Jørgensen, H. G., Venkatpurwar, V. P., Zhou, B., Rodrigues Hoffmann, A., Basu, R., Guo, S. and Majeti, N. V. R. K. (2017). Nano-curcumin safely prevents streptozotocin-induced inflammation and apoptosis in pancreatic beta cells for effective management of type 1 diabetes mellitus. *Br J Pharmacol*., 174(13): 2074-2084.

Gaspar, J. M., Baptista, F. I., Macedo, M. P. and Ambrósio, A. F. (2016). Inside the diabetic brain: role of different players involved in cognitive decline. *ACS Chem Neurosci*., 7(2): 131-42.

Gautam, P., Anstey, K. J., Wen, W., Sachdev, P. S. and Cherbuin, N. (2015). Cortical gyrification and its relationships with cortical volume, cortical thickness, and cognitive performance in healthy mid-life adults. *Behav Brain Res*., 287: 331-9.

Gehling, D. J., Lecka-Czernik, B. and Ebraheim, N. A. (2016). Orthopedic complications in diabetes. *Bone*, 82: 79-92.

Gerich, J. E. (2010). Role of the kidney in normal glucose homeostasis and in the hyperglycaemia of diabetes mellitus: therapeutic implications. *Diabet Med*., 27(2): 136-42.

Giacco, F. and Brownlee, M. (2010). Oxidative stress and diabetic complications. *Circ Res.*, 107(9): 1058-70.

Giambartolomei, G. H., Arriola Benitez, P. C. and Delpino, M. V. (2017). Brucella and osteoarticular cell activation: partners in crime. *Front Microbiol.*, 8: 256.

Giannarelli, R., Aragona, M., Coppelli, A. and Del Prato, S. (2003). Reducing insulin resistance with metformin: the evidence today. *Diabetes Metab.*, 29: 6S28-35.

Giordano, C., Karasik, O., King-Morris, K. and Asmar, A. (2015) Uric acid as a marker of kidney disease: review of the current literature. *Disease Markers*, 2015: 382918.

Giugliano, D., Ceriello, A. and Esposito, K. (2008). Glucose metabolism and hyperglycemia. *Am J Clin Nutr.*, 87: 217S-222S.

Gnudi, L. and Karalliedde, J. (2015). Beat it early: putative renoprotective haemodynamic effects of oral hypoglycaemic agents. *Nephrol Dial Transplant.*, 0: 1-8.

Gomathi, D., Kalaiselvi, M., Ravikumar, G., Devaki, K. and Uma, C. (2014). Evaluation of antioxidants in the kidney of streptozotocin induced diabetic rats. *Indian J Clin Biochem.*, 29(2): 221-6.

Gomes, A., Saha, P. P., Bhowmik, T., Dasgupta, A. K. and Dasgupta, S. C. (2016). Protection against osteoarthritis in experimental animals by nanogold conjugated snake venom protein toxin gold nanoparticle-Naja kaouthia cytotoxin 1. *Indian J Med Res.*, 144(6): 910-917.

Gómez-Pinilla, F. (2008). Brain foods: the effects of nutrients on brain function. *Nat Rev Neurosci.*, 9(7): 568-78.

Grieb, P. (2016). Intracerebroventricular streptozotocin injections as a model of Alzheimer's disease: in search of a relevant mechanism. *Mol Neurobiol.*, 53(3): 1741-1752.

Griel, A. E., Kris-Etherton, P. M., Hilpert, K. F., Zhao, G., West, S. G. and Corwin, R. L. (2007). An increase in dietary n-3 fatty acids decreases a marker of bone resorption in humans. *Nutr J.*, 6: 2.

Grünblatt, E., Salkovic-Petrisic, M., Osmanovic, J., Riederer, P. and Hoyer, S. (2007). Brain insulin system dysfunction in streptozotocin intracerebroventricularly treated rats generates hyperphosphorylated tau protein. *J Neurochem.*, 101(3): 757-70.

Guéraud, F., Taché, S., Steghens, J. P., Milkovic, L., Borovic-Sunjic, S., Zarkovic, N., Gaultier, E., Naud, N., Héliès-Toussaint, C., Pierre, F. and Priymenko, N. (2015). Dietary polyunsaturated fatty acids and heme iron induce oxidative stress biomarkers and a cancer promoting environment in the colon of rats. *Free Radic Biol Med*., 83: 192-200.

Gundberg, C. M., Lian, J. B. and Booth, S. L. (2012). Vitamin K-dependent carboxylation of osteocalcin: friend or foe? *Adv Nutr*., 3(2): 149-57.

Guntur, A. R. and Rosen, C. J. (2012). Bone as an endocrine organ. *Endocr Pract*., 18(5): 758-62.

Guo, C., Sun, L., Chen, X. and Zhang, D. (2013). Oxidative stress, mitochondrial damage and neurodegenerative diseases. *Neural Regen Res*., 8(21): 2003-2014.

Guo, H., Pan, C., Chang, B., Wu, X., Guo, J., Zhou, Y., Liu, H., Zhu, Z., Chang, B. and Chen, L. (2016). Triptolide improves diabetic nephropathy by regulating Th cell balance and macrophage infiltration in rat models of diabetic nephropathy. *Exp Clin Endocrinol Diabetes*, 124(6): 389-98.

Guo, J. D., Li, L., Shi, Y. M., Wang, H. D. and Hou, S. X. (2013). Hydrogen water consumption prevents osteopenia in ovariectomized rats. *Br J Pharmacol*., 168(6): 1412-20.

Gupta, R., Sharma, A. K., Sharma, M. C. and Gupta, R. S. (2012). Antioxidant activity and protection of pancreatic β-cells by embelin in streptozotocin-induced diabetes. *J Diabetes*., 4(3): 248-56.

Gurukar, M. S. A., Mahadevamma, S. and Chilkunda, N. D. (2013). Renoprotective effect of *Coccinia indica* fruits and leaves in experimentally induced diabetic rats. *J Med Food*., 16(9): 839-846.

Guzel, S and Gunes, N. (2014). Correlations between endogen amylin hormone and some hormonal, biochemical and bone parameters in pullets. *Rev. Bras. Cienc. Avic*., 16: 375-380.

Haast, R. A. and Kiliaan, A. J. (2015). Impact of fatty acids on brain circulation, structure and function. *Prostaglandins Leukot Essent Fatty Acids*, 92: 3-14.

Hafizur, R. M., Fatima, N. and Shaukat, S. (2015). Immunohistochemical evidence of pancreatic β-cell regeneration in streptozotocin-induced type 2 diabetic rats treated with *Gymnema sylvestre* Extract. *J Cytol Histol*., 6: 342.

Haider, S., Ahmed, S., Tabassum, S., Memon, Z., Ikram, M. and Haleem, D. J. (2013). Streptozotocin-induced insulin deficiency leads to development of behavioral deficits in rats. *Acta Neurol Belg*., 113(1): 35-41.

Hajjar, T., Goh, Y. M., Rajion, M. A., Vidyadaran, S., Li, T. A. and Ebrahimi, M. (2013). Alterations in neuronal morphology and synaptophysin expression in the rat brain as a result of changes in dietary n-6: n-3 fatty acid ratios. *Lipids Health Dis*., 12: 113.

Hale, L. J. and Coward, R. J. (2013). Insulin signalling to the kidney in health and disease. *Clin Sci (Lond)*., 124(6): 351-70.

Hamada, S., Satoh, K., Hirota, M., Kimura, K., Kanno, A., Masamune, A. and Shimosegawa, T. (2007). Bone morphogenetic protein 4 induces epithelial-mesenchymal transition through MSX2 induction on pancreatic cancer cell line. *J Cell Physiol*., 213(3): 768-74.

Han, X., Tao, Y. L., Deng, Y. P., Yu, J. W., Cai, J., Ren, G. F., Sun, Y. N. and Jiang, G. J. (2017). Metformin ameliorates insulitis in STZ-induced diabetic mice. *PeerJ*., 5: e3155.

Hardcastle, S. A., Dieppe, P., Gregson, C. L., Davey Smith, G. and Tobias, J. H. (2015). Osteoarthritis and bone mineral density: are strong bones bad for joints? *Bonekey Rep*., 4: 624.

Hardwick, R. N., Fisher, C. D., Canet, M. J., Lake, A. D. and Cherrington, N. J. (2010). Diversity in antioxidant response enzymes in progressive stages of human nonalcoholic fatty liver disease. *Drug Metab Dispos*., 38(12): 2293-301.

Harshman, S. W., Young, N. L., Parthun, M. R. and Freitas, M. A. (2013). H1 histones: current perspectives and challenges. *Nucleic Acids Res*., 41(21): 9593-609.

Hartweg, J., Perera, R., Montori, V., Dinneen, S., Neil, H. A. and Farmer, A. (2008). Omega-3 polyunsaturated fatty acids (PUFA) for type 2 diabetes mellitus. *Cochrane Database Syst Rev*., 1: CD003205.

Hashimoto, M., Inoue, T., Katakura, M., Tanabe, Y., Hossain, S., Tsuchikura, S. and Shido, O. (2013). Prescription n-3 fatty acids, but not eicosapentaenoic acid alone, improve reference memory-related learning ability by increasing brain-derived neurotrophic factor levels in SHR.Cg-Leprcp/NDmcr rats, a metabolic syndrome model. *Neurochem Res*., 38(10): 2124-2135.

He, L. and Wondisford, F. E. (2015). Metformin action: concentrations matter. *Cell Metab*., 21(2): 159-62.

He, M., Min, J. W., Kong, W. L., He, X. H., Li, J. X. and Peng, B. W. (2016). A review on the pharmacological effects of vitexin and isovitexin. *Fitoterapia*, 115: 74-85.

He, Q., Li, Q., Zhao, J., Wu, T., Ji, L., Huang, G. and Ma, F. (2016). Relationship between plasma lipids and mild cognitive impairment in the elderly Chinese: a case-control study. *Lipids Health Dis*., 15(1): 146.

Hendrich, S. (2010). (n-3) Fatty acids: clinical trials in people with type 2 diabetes. *Adv Nutr*., 1: 3-7.

Herath, P. M., Cherbuin, N., Eramudugolla, R. and Anstey, K. J. (2016). The effect of diabetes medication on cognitive function: evidence from the PATH through life study. *Biomed Res Int*., 2016: 7208429.

Heraud, P., Ng, E. S., Caine, S., Yu, Q. C., Hirst, C., Mayberry, R., Bruce, A., Wood, B. R., McNaughton, D., Stanley, E. G. and Elefanty, A. G. (2010). Fourier transform infrared microspectroscopy identifies early lineage commitment in differentiating human embryonic stem cells. *Stem Cell Res*., 4(2): 140-7.

Hiragushi, K., Wada, J., Eguchi, J., Matsuoka, T., Yasuhara, A., Hashimoto, I., Yamashita, T., Hida, K., Nakamura, Y., Shikata, K., Minamino, N., Kangawa, K. and Makino, H. (2004). The role of adrenomedullin and receptors in glomerular hyperfiltration in streptozotocin-induced diabetic rats. *Kidney Int*., 65(2): 540-50.

Hirata, Y., Yamamoto, E., Tokitsu, T., Fujisue, K., Kurokawa, H., Sugamura, K., Sakamoto, K., Tsujita, K., Tanaka, T., Kaikita, K., Hokimoto, S., Sugiyama, S. and Ogawa, H. (2015). The pivotal role of a novel biomarker of reactive oxygen species in chronic kidney disease. *Medicine (Baltimore)*, 94(25): e1040.

Ho, N., Sommers, M. S. and Lucki, I. (2013). Effects of diabetes on hippocampal neurogenesis: links to cognition and depression. *Neurosci Biobehav Rev*., 37(8): 1346-62.

Hoarau, E., Chandra, V., Rustin, P., Scharfmann, R. and Duvillie, B. (2014). Pro-oxidant/antioxidant balance controls pancreatic β-cell differentiation through the ERK1/2 pathway. *Cell Death Dis*., 5: e1487.

Holman, H. Y. N., Martin, M. C. and McKinney, W. R. (2003). Tracking chemical changes in a live cell: biomedical applications of SR-FTIR spectromicroscopy. *Spectroscopy*, 17: 139-159.

Horcajada-Molteni, M. N., Chanteranne, B., Lebecque, P., Davicco, M. J., Coxam, V., Young, A. and Barlet, J. P. (2001). Amylin and bone metabolism in streptozotocin-induced diabetic rats. *J Bone Miner Res*., 16(5): 958-65.

Hosokawa, M., Dolci, W. and Thorens, B. (2001). Differential sensitivity of GLUT1- and GLUT2-expressing beta cells to streptozotocin. *Biochem Biophys Res Commun*., 289(5): 1114-7.

Hosseini, A., Shafiee-Nick, R. and Ghorbani, A. (2015). Pancreatic beta cell protection/regeneration with phytotherapy. *Brazilian Journal of Pharmaceutical Science*, 51(1): 1-16.

Hu, Y., Li, L., Xu, Y., Yu, T., Tong, G., Huang, H., Bi, Y., Weng, J. and Zhu, D. (2011). Short-term intensive therapy in newly diagnosed type 2 diabetes partially restores both insulin sensitivity and β-cell function in subjects with long-term remission. *Diabetes Care*, 34(8): 1848-53.

Huang, M., Gao, L., Yang, L., Lin, F. and Lei, H. (2012). Abnormalities in the brain of streptozotocin-induced type 1 diabetic rats revealed by diffusion tensor imaging. *Neuroimage Clin*., 1(1): 57-65.

Huang, T., Wahlqvist, M. L. and Li, D. (2012). Effect of n-3 polyunsaturated fatty acid on gene expression of the critical enzymes involved in homocysteine metabolism. *Nutr J*., 11: 6.

Huang, Y., Dessel, J. V., Depypere, M., EzEldeen, M., Iliescu, A. A., Santos, E. D., Lambrichts, I., Liang, X. and Jacobs, R. (2014). Validating cone-beam computed tomography for peri-implant bone morphometric analysis. *Bone Research*, 2: 14010.

Hung, C. C., Lin, H. Y., Lee, J. J., Lim, L. M., Chiu, Y. W., Chiang, H. P., Hwang, S. J. and Chen, H. C. (2016). Glycosuria and renal outcomes in patients with nondiabetic advanced chronic kidney disease. *Sci Rep*., 6: 39372.

Hussein, Z., Taher, S. W., Gilcharan Singh, H. K. and Chee Siew Swee, W. (2015). Diabetes care in Malaysia: problems, new models, and solutions. *Ann Glob Health*, 81(6): 851-62.

Hwang, H. S. and Kim, H. A. (2015). Chondrocyte apoptosis in the pathogenesis of osteoarthritis. *Int J Mol Sci*., 16(11): 26035-54.

Hwang, W. M., Bak, D. H., Kim, D. H., Hong, J. Y., Han, S. Y., Park, K. Y., Lim, K., Lim, D. M. and Kang, J. G. (2015). Omega-3 polyunsaturated fatty acids may attenuate streptozotocin-induced pancreatic β-cell death via autophagy activation in fat1 transgenic mice. *Endocrinol Metab (Seoul)*., 30(4): 569-75.

Hwang, M., Tudorascu, D. L., Nunley, K., Karim, H., Aizenstein, H. J., Orchard, T. J. and Rosano, C. (2016). Brain activation and psychomotor speed in middle-aged patients with type 1 diabetes: relationships with hyperglycemia and brain small vessel disease. *Journal of Diabetes Research*, 2016: 9571464.

Ikeda, T., Iwata, K. and Murakami, H. (2000). Inhibitory effect of metformin on intestinal glucose absorption in the perfused rat intestine. *Biochem Pharmacol*., 59(7): 887-90.

Ilatovskaya, D., Palygin, O. and Staruschenko, A. (2015). Hydrogen peroxide evokes acute calcium influx in the podocytes of murine glomeruli. *The FASEB Journal*, 29: 666.16.

Imig, J. D. and Ryan, M. J. (2013). Immune and inflammatory role in renal disease. *Compr Physiol*., 3(2): 957-976.

Intine, R. V. and Sarras, M. P. (2012). Metabolic memory and chronic diabetes complications: potential role for epigenetic mechanisms. *Curr Diab Rep*., 12(5): 551-9.

Isik, A. T., Celik, T., Ulusoy, G., Ongoru, O., Elibol, B., Doruk, H., Bozoglu, E., Kayir, H., Mas, M. R. and Akman, S. (2009). Curcumin ameliorates impaired insulin/IGF signalling and memory deficit in a streptozotocin-treated rat model. *Age (Dordr)*., 31(1): 39-49.

Iurlaro, R., Püschel, F., León-Annicchiarico, C. L., O'Connor, H., Martin, S. J., Palou-Gramón, D., Lucendo, E. and Muñoz-Pinedo, C. (2017). Glucose deprivation induces ATF4-mediated apoptosis through TRAIL death receptors. *Mol Cell Biol*., 37(10): e00479-16.

Jackuliak, P. and Payer, J. (2014). Osteoporosis, fractures, and diabetes. *Int J Endocrinol*., 2014: 820615.

Jaiswal, N., Maurya, C. K., Pandey, J., Rai, A. K. and Tamrakar, A. K. (2015). Fructose-induced ROS generation impairs glucose utilization in L6 skeletal muscle cells. *Free Radic Res*., 49(9): 1055-68.

Jiang, Y., Huang, W., Wang, J., Xu, Z., He, J., Lin, X., Zhou, Z. and Zhang, J. (2014). Metformin plays a dual role in MIN6 pancreatic β cell function through AMPK-dependent autophagy. *Int J Biol Sci*., 10(3): 268-77.

Jiao, H., Xiao, E. and Graves, D. T. (2015). Diabetes and its effect on bone and fracture healing. *Curr Osteoporos Rep*., 13(5): 327-35.

Jivada, N. and Rabieib, Z. (2014). A review study on medicinal plants used in the treatment of learning and memory impairments. *Asian Pacific Journal of Tropical Biomedicine*, 4(10): 780-789.

Johns, E. J., Kopp, U. C. and DiBona, G. F. (2011). Neural control of renal function. *Compr Physiol*., 1(2): 731-67.

Johnson, R. J., Nakagawa, T., Jalal, D., Sánchez-Lozada, L. G., Kang, D. H. and Ritz, E. (2013). Uric acid and chronic kidney disease: which is chasing which? *Nephrol Dial Transplant*., 28(9): 2221-8.

Jones, G., Dwyer, T., Hynes, K. L., Parameswaran, V., Udayan, R. and Greenaway, T. M. (2007). A prospective study of urinary electrolytes and bone turnover in adolescent males. *Clin Nutr*., 26(5): 619-23.

Jurgens, C. A., Toukatly, M. N., Fligner, C. L., Udayasankar, J., Subramanian, S. L., Zraika, S., Aston-Mourney, K., Carr, D. B., Westermark, P., Westermark, G. T., Kahn, S. E. and Hull, R. L. (2011). β-cell loss and β-cell apoptosis in human type 2 diabetes are related to islet amyloid deposition. *Am J Pathol*., 178(6): 2632-40.

Kalman, D. S., Schwartz, H. I., Feldman, S. and Krieger, D. R. (2013). Efficacy and safety of *Elaeis guineensis* and *Ficus deltoidea* leaf extracts in adults with pre-diabetes. *Nutrition Journal*, 12: 36.

Kamat, P. K. (2015). Streptozotocin induced Alzheimer's disease like changes and the underlying neural degeneration and regeneration mechanism. *Neural Regen Res*., 10(7): 1050-2.

Kanazawa, I. (2015). Osteocalcin as a hormone regulating glucose metabolism. *World J Diabetes*, 6(18): 1345-1354.

Kang, J. X. (2011). The omega-6/omega-3 fatty acid ratio in chronic diseases: animal models and molecular aspects. *World Rev Nutr Diet*., 102: 22-9.

Kanwar, M. and Kowluru, R. A. (2009). Role of glyceraldehyde 3-phosphate dehydrogenase in the development and progression of diabetic retinopathy. *Diabetes*, 58(1): 227-234.

Kaplan, R. J., Greenwood, C. E., Winocur, G. and Wolever T. M. (2000). Cognitive performance is associated with glucose regulation in healthy elderly persons and can be enhanced with glucose and dietary carbohydrates. *Am J Clin Nutr*., 72(3): 825-36.

Karachalias, N., Babaei-Jadidi, R., Ahmed, N. and Thornalley, P. J. (2003). Accumulation of fructosyl-lysine and advanced glycation end products in the kidney, retina and peripheral nerve of streptozotocin-induced diabetic rats. *Biochem Soc Trans*., 31: 1423-5.

Karasu, Ç., Cumaoğlu, A., Gürpinar, A. R., Kartal, M., Kovacikova, L., Milackova, I. and Stefek, M. (2012). Aldose reductase inhibitory activity and antioxidant capacity of pomegranate extracts. *Interdiscip Toxicol*., 5(1): 15-20.

Kashihara, N., Haruna, Y., Kondeti, V. K. and Kanwar, Y. S. (2010). Oxidative stress in diabetic nephropathy. *Curr Med Chem*., 17(34): 4256-69.

Katiyar, C., Gupta, A., Kanjilal, S. and Katiyar, S. (2012). Drug discovery from plant sources: An integrated approach. *Ayu*., 33(1): 10-19.

Kaung, H. C. (1983). Effect of glucose on beta cell proliferation and population size in organ culture of foetal and neonatal rat pancreases. *J Embryol Exp Morphol*., 75: 303-12.

Kaur, G., Padiya, R., Adela, R., Putcha, U. K., Reddy, G. S., Reddy, B. R., Kumar, K. P., Chakravarty, S. and Banerjee, S. K. (2016). Garlic and resveratrol attenuate diabetic complications, loss of β-cells, pancreatic and hepatic oxidative stress in streptozotocin-induced diabetic rats. *Front Pharmacol*., 7: 360.

Kaur, R., Sodhi, R. K., Aggarwal, N., Kaur, J. and Jain, U. K. (2016). Renoprotective effect of lansoprazole in streptozotocin-induced diabetic nephropathy in wistar rats. *Naunyn Schmiedebergs Arch Pharmacol*., 389(1): 73-85.

Kaur, U., Chakrabarti, S. S. and Gambhir, I. S. (2016). Zoledronate induced hypocalcemia and hypophosphatemia in osteoporosis: a cause of concern. *Curr Drug Saf*., 11(3): 267-9.

Kawamura, T., Umemura, T. and Hotta, N. (2015). Curious relationship between cognitive impairment and diabetic retinopathy. *J Diabetes Investig*., 6(1): 21-23.

Kawasaki, E. (2014). Type 1 diabetes and autoimmunity. *Clin Pediatr Endocrinol*., 23(4): 99-105.

Kazemian, M., Abad, M., Haeri, M. R., Ebrahimi, M. and Heidari, R. (2015). Anti-diabetic effect of *Capparis spinosa* L. root extract in diabetic rats. *Avicenna J Phytomed*., 5(4): 325-332.

Khajehpour, M., Dashnau, J. L. and Vanderkooi, J. M. (2006). Infrared spectroscopy used to evaluate glycosylation of proteins. *Anal Biochem*., 348(1): 40-8.

Khan, R. A., Khan, M. R. and Sahreen, S. (2012). Brain antioxidant markers, cognitive performance and acetylcholinesterase activity of rats: efficiency of Sonchus asper. *Behav Brain Funct*., 8: 21.

Khanmohammadi, M., Ghasemi, K., Garmarudi, A. B. and Ramin, M. (2015). Diagnostic prediction of renal failure from blood serum analysis by FTIR spectrometry and chemometrics. *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy*, 136: 1782-1785.

Kharouta, M., Miller, K., Kim, A., Wojcik, P., Kilimnik, G., Dey, A., Steiner, D. F. and Hara, M. (2009). No mantle formation in rodent islets - the prototype of islet revisited. *Diabetes Res Clin Pract*., 85(3): 252-7.

Kiba, T. (2004). Relationships between the autonomic nervous system and the pancreas including regulation of regeneration and apoptosis: recent developments. *Pancreas*, 29(2): e51-8.

Kim, H. C., Cho, Y. J., Ahn, C. W., Park, K. S., Kim, J. C., Nam, J. S., Im, Y. S., Lee, J. E., Lee, S. C. and Lee, H. K. (2009). Nerve growth factor and expression of its receptors in patients with diabetic neuropathy. *Diabet Med*., 26(12): 1228-34.

Kim, H., Zamel, R., Bai, X. H. and Liu, M. (2013). PKC activation induces inflammatory response and cell death in human bronchial epithelial cells. *PLoS One*., 8(5): e64182.

Kim, J. Y., Lee, H., Lee, S. J., Jung, Y. H., Yoo, D. Y., Hwang, I. K., Seong, J. K., Ryu, J. M. and Han, H. J. (2017). Palmitic acid-BSA enhances amyloid-β production through GPR40-mediated dual pathways in neuronal cells: involvement of the Akt/mTOR/HIF-1α and Akt/NF-κB pathways. *Sci Rep*., 7(1): 4335.

Kim, K. S., Oh, D. H., Kim, J. Y., Lee, B. G., You, J. S., Chang, K. J., Chung, H. J., Yoo, M. C., Yang, H. I., Kang, J. H., Hwang, Y. C., Ahn, K. J., Chung, H. Y. and Jeong, I. K. (2012). Taurine ameliorates hyperglycemia and dyslipidemia by reducing insulin resistance and leptin level in Otsuka Long-Evans Tokushima fatty (OLETF) rats with long-term diabetes. *Exp Mol Med*., 44(11): 665-73.

King, A. J. (2012). The use of animal models in diabetes research. *Br J Pharmacol*., 166(3): 877-94..

King, K. B. and Rosenthal, A. K. (2015). The adverse effects of diabetes on osteoarthritis: update on clinical evidence and molecular mechanisms. *Osteoarthritis Cartilage*, 23(6): 841-50.

Kingsbury, M. A., Rehen, S. K., Contos, J. J., Higgins, C. M. and Chun, J. (2003). Non-proliferative effects of lysophosphatidic acid enhance cortical growth and folding. *Nat Neurosci*., 6(12): 1292-9.

Kiran, G., Nandini, C. D., Ramesh, H. P. and Salimath, P. V. (2012). Progression of early phase diabetic nephropathy in streptozotocin-induced diabetic rats: evaluation of various kidney-related parameters. *Indian J Exp Biol*., 50(2): 133-40.

Kishimoto, H., Akagi, M., Zushi, S., Teramura, T., Onodera, Y., Sawamura, T. and Hamanishi, C. (2010). Induction of hypertrophic chondrocyte-like phenotypes by oxidized LDL in cultured bovine articular chondrocytes through increase in oxidative stress. *Osteoarthritis Cartilage*, 18(10): 1284-90.

Klein, G. L. (2014). Insulin and bone: recent developments. *World J Diabetes*, 5(1): 14-16.

Kleinridders, A., Ferris, H., Cai, W. and Kahn, C. R. (2014). Insulin action in brain regulates systemic metabolism and brain function. *Diabetes*, 63(7): 2232-43.

Kodl, C. T. and Seaquist, E. R. (2008). Cognitive dysfunction and diabetes mellitus. *Endocr Rev*., 29(4): 494-511.

Koerte, I. K., Mayinger, M., Muehlmann, M., Kaufmann, D., Lin, A. P., Steffinger, D., Fisch, B., Rauchmann, B. S., Immler, S., Karch, S., Heinen, F. R., Ertl-Wagner, B., Reiser, M., Stern, R. A., Zafonte, R. and Shenton, M. E. (2016). Cortical thinning in former professional soccer players. *Brain Imaging Behav*., 10(3): 792-8.

Korol, D. L., Malin, E. L., Borden, K. A., Busby, R. A. and Couper-Leo, J. (2004). Shifts in preferred learning strategy across the estrous cycle in female rats. *Horm Behav*., 45(5): 330-8.

Korrapati, M. C., Shaner, B. E., Neely, B. A., Alge, J. L., Arthur, J. M. and Schnellmann, R. G. (2012). Diabetes-induced renal injury in rats is attenuated by suramin. *J Pharmacol Exp Ther*., 343(1): 34-43.

Kourkoumelis, N. and Tzaphlidou, M. (2010). Spectroscopic assessment of normal cortical bone: differences in relation to bone site and sex. *The Scientific World Journal*, 10: 402-412.

Kover, K., Yan, Y., Tong, P. Y., Watkins, D., Li, X., Tasch, J., Hager, M., Clements, M. and Moore, W. V. (2015). Osteocalcin protects pancreatic beta cell function and survival under high glucose conditions. *Biochem Biophys Res Commun*., 462(1): 21-6.

Krug, E. G. (2016). Trends in diabetes: sounding the alarm. *Lancet*, 387(10027): 1485-6.

Kruger, F. A., Skillman, T. G., Hamwi, G. J., Grubbs, R. C. and Danforth, N. (1960). The mechanism of action of hypoglycemic guanidine derivatives. *Diabete*s, 9: 170-3.

Kulkarni, D. K. (2017). Brain injury and the kidney*. J Neuroanaesthesiol Crit Care*., 3: 16-9.

Kulozik, F. and Hasslacher, C. (2013). Insulin requirements in patients with diabetes and declining kidney function: differences between insulin analogues and human insulin? *Ther Adv Endocrinol Metab*., 4(4): 113-121.

Kumar, A., Mittal, S., Orito, S., Ishitani, K. and Ohta, H. (2010). Impact of dietary intake, education, and physical activity on bone mineral density among North Indian women. *J Bone Miner Metab*., 28(2): 192-201.

Kumar, B. S., Ravisankar, A., Mohan, A., Kumar, D. P., Katyarmal, D. T., Sachan, A. and Sarma, K. V. (2015). Effect of oral hypoglycaemic agents on bone metabolism in patients with type 2 diabetes mellitus and occurrence of osteoporosis. *Indian J Med Res*., 141(4): 431-7.

Kumsta, C., Thamsen, M. and Jakob, U. (2011). Effects of oxidative stress on behavior, physiology, and the redox thiol proteome of *Caenorhabditis elegans*. *Antioxid Redox Signal*, 14(6): 1023-37.

Kwak, H. J., Liu, P., Bajrami, B., Xu, Y., Park, S. Y., Nombela-Arrieta, C., Mondal, S., Sun, Y., Zhu, H., Chai, L., Silberstein, L. E., Cheng, T. and Luo, H. R. (2015). Myeloid cell-derived reactive oxygen species externally regulate the proliferation of myeloid progenitors in emergency granulopoiesis. *Immunity*, 42(1): 159-71.

Labak, M., Foniok, T., Kirk, D., Rushforth, D., Tomanek, B., Jasiński, A. and Grieb, P. (2010). Metabolic changes in rat brain following intracerebroventricular injections of streptozotocin: a model of sporadic Alzheimer's disease. *Acta Neurochir Suppl*., 106: 177-81.

Łabuzek, K., Suchy, D., Gabryel, B., Bielecka, A., Liber, S. and Okopień, B. (2010). Quantification of metformin by the HPLC method in brain regions, cerebrospinal fluid and plasma of rats treated with lipopolysaccharide. *Pharmacol Rep*., 62(5): 956-65.

Lang-Lazdunski, L., Blondeau, N., Jarretou, G., Lazdunski, M. and Heurteaux, C. (2003). Linolenic acid prevents neuronal cell death and paraplegia after transient spinal cord ischemia in rats. *Journal of Vascular Surgery*, 38(3): 564-575.

Lavelle, G. M., White, M. M., Browne, N., McElvaney, N. G. and Reeves, E. P. (2016). Animal models of cystic fibrosis pathology: phenotypic parallels and divergences. *BioMed Research International*, 2016: 5258727.

Lawrence, C. F., Margetts, M. B., Menting, J. G., Smith, N. A., Smith, B. J., Ward, C. W. and Lawrence, M. C. (2016). Insulin mimetic peptide disrupts the primary binding site of the insulin receptor. *J Biol Chem*., 291(30): 15473-81.

Lawson, C. J., Homewood, J. and Taylor, A. J. (2002). The effects of L-glucose on memory in mice are modulated by peripherally acting cholinergic drugs. *Neurobiol Learn Mem.,* 77(1): 17-28.

Lazzarini, P. A., Gurr, J. M., Rogers, J. R., Schox, A. and Bergin, S. M. (2013). Australia's 'silent pandemic' of diabetes complications: where do feet stand in this pandemic? *J Foot Ankle Res*., 6: O25.

Lebovitz, H. E. (2011). Insulin: potential negative consequences of early routine use in patients with type 2 diabetes. *Diabetes Care*, 34: S225-30.

Lee, B., Sur, B., Shim, J., Hahm, D. H. and Lee, H. (2014). Acupuncture stimulation improves scopolamine-induced cognitive impairment via activation of cholinergic system and regulation of BDNF and CREB expressions in rats. *BMC Complement Altern Med*., 14: 338.

Lee, C., An, D. and Park, J. (2016). Hyperglycemic memory in metabolism and cancer. *Horm Mol Biol Clin Investig*., 26(2): 77-85.

Lee, H. T., Kim, M., Jan, M. and Emala, C. W. (2006). Anti-inflammatory and antinecrotic effects of the volatile anesthetic sevoflurane in kidney proximal tubule cells. *Am J Physiol Renal Physiol*., 291(1): F67-78.

Lee, J. and Vasikaran, S. (2012). Current recommendations for laboratory testing and use of bone turnover markers in management of osteoporosis. *Ann Lab Med*., 32(2): 105-112.

Lee, J. H., Lee, Y. H., Jung, K. H., Kim, M. K., Jang, H. W., Kim, T. K., Kim, H. J., Jo, Y. S., Shong, M., Lee, T. Y. and Ku, B. J. (2010). Bone mineral density in prediabetic men. *Korean Diabetes J*., 34(5): 294-302.

Lee, S. H., Zabolotny, J. M., Huang, H., Lee, H. and Kim, Y. B. (2016). Insulin in the nervous system and the mind: Functions in metabolism, memory, and mood. *Mol Metab*., 5(8): 589-601.

Lee, Y. J., Hong, J. Y., Kim, S. C., Joo, J. K., Na, Y. J. and Lee, K. S. (2015). The association between oxidative stress and bone mineral density according to menopausal status of Korean women. *Obstet Gynecol Sci*., 58(1): 46-52.

Leidig-Bruckner, G., Grobholz, S., Bruckner, T., Scheidt-Nave, C., Nawroth, P. and Schneider, J. G. (2014). Prevalence and determinants of osteoporosis in patients with type 1 and type 2 diabetes mellitus. *BMC Endocr Disord*., 14: 33.

Leisman, G., Moustafa, A. A. and Shafir, T. (2016). Thinking, walking, talking: integratory motor and cognitive brain function. *Front Public Health*, 4: 94.

Lenzen, S. (2008). The mechanisms of alloxan- and streptozotocin-induced diabetes. *Diabetologia*, 51(2): 216-26.

Lepetsos, P. and Papavassiliou, A. G. (2016). ROS/oxidative stress signaling in osteoarthritis. *Biochim Biophys Acta*., 1862(4): 576-91.

L'Episcopo, F., Drouin-Ouellet, J., Tirolo, C., Pulvirenti, A., Giugno, R., Testa, N., Caniglia, S., Serapide, M. F., Cisbani, G., Barker, R. A., Cicchetti, F. and Marchetti, B. (2016). GSK-3β-induced Tau pathology drives hippocampal neuronal cell death in Huntington's disease: involvement of astrocyte-neuron interactions. *Cell Death Dis*., 7: e2206.

Lerner, U. H. (2012). Osteoblasts, osteoclasts, and osteocytes: unveiling their intimate-associated responses to applied orthodontic forces. *Seminars in Orthodontics,* 18(4): 237-248.

Leto, D. and Saltiel, A. R. (2012). Regulation of glucose transport by insulin: traffic control of GLUT4. *Nat Rev Mol Cell Biol*., 13(6): 383-96.

Levant, B., Ozias, M. K., Guilford, B. L. and Wright, D. E. (2013). Streptozotocin-induced diabetes partially attenuates the effects of a high-fat diet on liver and brain fatty acid composition in mice. *Lipids*, 48(9): 939-948.

Li, J., He, W., Liao, B. and Yang, J. (2015). FFA-ROS-P53-mediated mitochondrial apoptosis contributes to reduction of osteoblastogenesis and bone mass in type 2 diabetes mellitus. *Scientific Reports*, 5: 12724.

Li, J., Zhang, S., Zhang, L., Wang, R. and Wang, M. (2015). Effects of L-3-n-butylphthalide on cognitive dysfunction and NR2B expression in hippocampus of streptozotocin (STZ)-induced diabetic rats. *Cell Biochem Biophys*., 71(1): 315-22.

Li, P., Zhang, L., Tian, X. and Xing, J. (2014). Docosahexaenoic acid has an anti-diabetic effect in streptozotocin-induced diabetic mice. *Int J Clin Exp Med*., 7(9): 3021-9.

Li, S., Yan, T., Yang, J. Q., Oberley, T. D. and Oberley, L. W. (2000). The role of cellular glutathione peroxidase redox regulation in the suppression of tumor cell growth by manganese superoxide dismutase. *Cancer Res*., 60(14): 3927-39.

Li, W., Maloney, R. E. and Aw, T. Y. (2015). High glucose, glucose fluctuation and carbonyl stress enhance brain microvascular endothelial barrier dysfunction: implications for diabetic cerebral microvasculature. *Redox Biol*., 5: 80-90.

Li, W., Zhu, L. H., Wang, E. B., Ye, Z. C., Lin, J., Guo, L. H., Luo, F. H., Liu, X. H., Fang, X. and Shen, S. X. (2004). Effect of two human growth hormone receptor antagonists on glomerulosclerosis in streptozotocin-induced diabetic rats. *Acta Pharmacol Sin*., 25(4): 490-5.

Li, X., Guo, Y., Yan, W., Snyder, M, P. and Li, X. (2015). Metformin improves diabetic bone health by re-balancing catabolism and nitrogen disposal. *PLoS One*, 10(12): e0146152.

Li, Y., Reddy, M. A., Miao, F., Shanmugam, N., Yee, J. K., Hawkins, D., Ren, B. and Natarajan, R. (2008). Role of the histone H3 lysine 4 methyltransferase, SET7/9, in the regulation of NF-κB-dependent inflammatory genes. *The Journal of Biological Chemistry*, 283: 26771-26781.

Liakat, S., Bors, K. A., Xu, L., Woods, C. M., Doyle, J. and Gmachl, C. F. (2014). Noninvasive *in vivo* glucose sensing on human subjects using mid-infrared light. *Biomed Opt Express*, 5(7): 2397-404.

Liamis, G., Liberopoulos, E., Barkas, F. and Elisaf, M. (2014). Diabetes mellitus and electrolyte disorders. *World J Clin Cases*, 2(10): 488-496.

Liang, W., Luo, Z., Ge, S., Li, M., Du, J., Yang, M., Yan, M., Ye, Z. and Luo, Z. (2011). Oral administration of quercetin inhibits bone loss in rat model of diabetic osteopenia. *Eur J Pharmacol*., 670(1): 317-24.

Liberini, C. G., Borner, T., Boyle, C. N. and Lutz, T. A. (2016). The satiating hormone amylin enhances neurogenesis in the area postrema of adult rats. *Mol Metab*., 5(10): 834-43.

Liu, D., Huang, P., Li, X., Ge, M., Luo, G. and Hei, Z. (2014). Using inflammatory and oxidative biomarkers in urine to predict early acute kidney injury in patients undergoing liver transplantation. *Biomarkers*, 19(5): 424-9.

Liu, H. Y., Cao, S. Y., Hong, T., Han, J., Liu, Z. and Cao, W. (2009). Insulin is a stronger inducer of insulin resistance than hyperglycemia in mice with type 1 diabetes mellitus (T1DM). *The Journal of Biological Chemistry*, 284: 27090-27100.

Liu, R., Bal, H. S., Desta, T., Krothapalli, N., Alyassi, M., Luan, Q. and Graves, D. T. (2006). Diabetes enhances periodontal bone loss through enhanced resorption and diminished bone formation. *J Dent Res*., 85(6): 510-4.

Liu, T., Lipnicki, D. M., Zhu, W., Tao, D., Zhang, C., Cui, Y., Jin, J. S., Sachdev, P. S. and Wen, W. (2012). Cortical gyrification and sulcal spans in early stage Alzheimer's disease. *PLoS One*, 7(2): e31083.

Liu, X., Mo, Y., Gong, J., Li, Z., Peng, H., Chen, J., Wang, Q., Ke, Z. and Xie, J. (2016). Puerarin ameliorates cognitive deficits in streptozotocin-induced diabetic rats. *Metab Brain Dis*., 31(2): 417-23.

Liu, Z., Chen, H., Wu, P., Yao, Q., Cheng, H., Yu, W. and Liu, C. (2015). Flos *Puerariae* extract ameliorates cognitive impairment in streptozotocin-induced diabetic mice. *Evid Based Complement Alternat Med*., 2015: 873243.

Longnecker, D. (2014). *Anatomy and Histology of the Pancreas*. Pancreapedia: Exocrine Pancreas Knowledge Base.

Longo, A. B. and Ward, W. E. (2016). PUFAs, bone mineral density, and fragility fracture: findings from human studies. *Adv Nutr*., 7(2): 299-312.

Lorenzi, M. (2007). The polyol pathway as a mechanism for diabetic retinopathy: attractive, elusive, and resilient. *Exp Diabetes Res*., 2007: 61038.

Lowry, O. H., Rosebrough, N. J., Farr, A. L. and Randall, R. J. (1951). Protein measurement with the Folin phenol reagent. *J Biol Chem*., 193(1): 265-75.

Lu, J., Zang, J. and Li, H. (2013). Impact of three oral antidiabetic drugs on markers of β-cell function in patients with type 2 diabetes: a meta-analysis. *PLoS One*, 8(10): e76713.

Lucchesi, A. N., Cassettari, L. L. and Spadella, C. T. (2015). Alloxan-induced diabetes causes morphological and ultrastructural changes in rat liver that resemble the natural history of chronic fatty liver disease in humans. *Journal of Diabetes Research*, 2015: 494578.

Luders, E., Narr, K. L., Bilder, R. M., Szeszko, P. R., Gurbani, M. N., Hamilton, L., Toga, A. W. and Gaser, C. (2008). Mapping the relationship between cortical convolution and intelligence: effects of gender. *Cereb Cortex*., 18(9): 2019-2026.

Lutz, T. A. and Rand, J. S. (1996). Plasma amylin and insulin concentrations in normoglycemic and hyperglycemic cats. *Can Vet J*., 37(1): 27-34.

Ly, H. and Despa, F. (2015). Hyperamylinemia as a risk factor for accelerated cognitive decline in diabetes. *Expert Rev Proteomics*, 12(6):575-7.

Lyoo, I. K., Yoon, S., Jacobson, A. M., Hwang, J., Musen, G., Kim, J. E., Simonson, D. C., Bae, S., Bolo, N., Kim, D. J., Weinger, K., Lee, J. H., Ryan, C. M. and Renshaw, P. F. (2012). Prefrontal cortical deficits in type 1 diabetes mellitus: brain correlates of comorbid depression. *Arch Gen Psychiatry*, 69(12): 1267-76.

Macdonald, D. W., Squires, R. S., Avery, S. A., Adams, J., Baker, M., Cunningham, C. R., Heimann, N. B., Kooyman, D. L. and Seegmiller, R. E. (2013). Structural variations in articular cartilage matrix are associated with early-onset osteoarthritis in the spondyloepiphyseal dysplasia congenita (sedc) mouse. *Int J Mol Sci*., 14(8): 16515-31.

MacDonald, M. J., Ade, L., Ntambi, J. M., Ansari, I. U. and Stoker, S. W. (2015). Characterization of phospholipids in insulin secretory granules and mitochondria in pancreatic beta cells and their changes with glucose stimulation. *J Biol Chem*., 290(17): 11075-92.

MacDonald, M. J., Dobrzyn, A., Ntambi, J. and Stoker, S. W. (2008). The role of rapid lipogenesis in insulin secretion: Insulin secretagogues acutely alter lipid composition of INS-1 832/13 cells. *Arch Biochem Biophys*., 470(2): 153-62.

Madiraju, A. K., Erion, D. M., Rahimi, Y., Zhang, X. M., Braddock, D. T., Albright, R. A., Prigaro, B. J., Wood, J. L., Bhanot, S., MacDonald, M. J., Jurczak, M. J., Camporez, J. P., Lee, H. Y., Cline, G. W., Samuel, V. T., Kibbey, R. G. and Shulman, G. I. (2014). Metformin suppresses gluconeogenesis by inhibiting mitochondrial glycerophosphate dehydrogenase. *Nature*, 510(7506): 542-6.

Mahfoud, F., Schlaich, M., Kindermann, I., Ukena, C., Cremers, B., Brandt, M. C., Hoppe, U. C., Vonend, O., Rump, L. C., Sobotka, P. A., Krum, H., Esler, M. and Böhm, M. (2011). Effect of renal sympathetic denervation on glucose metabolism in patients with resistant hypertension: a pilot study. *Circulatio*n, 123(18): 1940-6.

Maléth, J. and Hegyi, P. (2016). Ca^{2+} toxicity and mitochondrial damage in acute pancreatitis: translational overview. *Philos Trans R Soc Lond B Biol Sci*., 371(1700): 20150425.

Malluche, H. H., Porter, D. S., Mawad, H., Monier-Faugere, M. C. and Pienkowski, D. (2013). Low-energy fractures without low T-scores characteristic of osteoporosis: a possible bone matrix disorder. *J Bone Joint Surg Am*., 95(19): e1391-6.

Mannucci, E., Dicembrini, I., Lauria, A. and Pozzilli, P. (2013). Is glucose control important for prevention of cardiovascular disease in diabetes? *Diabetes Care*, 36: S259-63.

Marín-Juez, R., Rovira, M., Crespo, D., van der Vaart, M., Spaink, H. P. and Planas, J. V. (2014). GLUT2-mediated glucose uptake and availability are required for embryonic brain development in zebrafish. *J Cereb Blood Flow Metab*., 35(1): 74-85.

Martins, J. B., Mendonça, V. A., Rocha, E. V., Tossige-Gomes, R., Fonseca, S. F., Costa, K. B., Avelar, N. C. P., Gomes, W. F. and Lacerda, A. C. R. (2015). Walking training decreases the plasma TBARS concentration in elderly women with knee osteoarthritis. *Ann Sports Med Res*., 2(5): 1034.

Marty, N., Dallaporta, M. and Thorens, B. (2007). Brain glucose sensing, counterregulation, and energy homeostasis. *Physiology (Bethesda)*, 22: 241-51.

Marycz, K., Tomaszewski, K. A., Kornicka, K., Henry, B. M., Wroński, S., Tarasiuk, J. and Maredziak, M. (2016). Metformin decreases reactive oxygen species, enhances osteogenic properties of adipose-derived multipotent mesenchymal stem cells *in vitro*, and increases bone density *in vivo. Oxid Med Cell Longev*., 2016: 9785890.

Matthes, F., Hettich, M. M., Ryan, D. P., Ehninger, D. and Krauss, S. (2015). The anti-diabetic drug metformin improves cognitive impairment and reduces amyloid-beta in a mouse model of Alzheimer’s disease. *Alzheimer's and Dementia*, 11(7): P845.

Matthews, D. R., Hosker, J. P., Rudenski, A. S., Naylor, B. A., Treacher, D. F. and Turner, R. C. (1985). Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia*, 28(7): 412-9.

McAuley, K. A., Williams, S. M., Mann, J. I., Walker, R. J., Lewis-Barned, N. J., Temple, L. A. and Duncan, A. W. (2001). Diagnosing insulin resistance in the general population. *Diabetes Care*, 24(3): 460-4.

McCrimmon, R. J., Ryan, C. M. and Frier, B. M. (2012). Diabetes and cognitive dysfunction. *Lancet*, 16: 2291-9.

Medina, A., Yamada, S., Hara, A., Hamamoto, K. and Kojima, I. (2013). Involvement of the parasympathetic nervous system in the initiation of regeneration of pancreatic β-cells. *Endocr J*., 60(5): 687-96.

Meier, J. J. and Bonadonna, R. C. (2013). Role of reduced β-cell mass versus impaired β-cell function in the pathogenesis of type 2 diabetes. *Diabetes Care*, 36: S113-S119.

Mellado-Gil, J. M., Cobo-Vuilleumier, N. and Gauthier, B. R. (2012). Islet -cell mass preservation and regeneration in diabetes mellitus: four factors with potential therapeutic interest. *Journal of Transplantation*, 2012: 230870.

Meng, F., Han, Y., Srisai, D., Belakhov, V., Farias, M., Xu, Y., Palmiter, R. D., Baasov, T. and Wu, Q. (2016). New inducible genetic method reveals critical roles of GABA in the control of feeding and metabolism. *Proc Natl Acad Sci U S A*., 113(13): 3645-50.

Mergenthaler, P., Lindauer, U., Dienel, G. A. and Meisel, A. (2013). Sugar for the brain: the role of glucose in physiological and pathological brain function. *Trends Neurosci*., 36(10): 587-97.

Meyers, E. E., Kronemberger, A., Lira, V., Rahmouni, K. and Stauss, H. M. (2016). Contrasting effects of afferent and efferent vagal nerve stimulation on insulin secretion and blood glucose regulation. *Physiol Rep*., 4(4): e12718.

Miller, P. D. (2012). Bone strength and surrogate markers: the first, second, and third fiddle. *Journal of Bone and Mineral Research*, 27: 1623-1626.

Miller, P. D. (2014). Chronic kidney disease and osteoporosis: evaluation and management. *Bonekey Rep*., 3: 542.

Mirmohammadlu, M., Hosseini, S. H., Kamalinejad, M., Esmaeili Gavgani, M., Noubarani, M. and Eskandari, M. R. (2015). Hypolipidemic, hepatoprotective and renoprotective effects of *Cydonia oblonga* mill. fruit in streptozotocin-induced diabetic rats. *Iran J Pharm Res*., 14(4): 1207-14.

Misbah, H., Aziz, A. A. and Aminudin, N. (2013). Antidiabetic and antioxidant properties of *Ficus deltoidea* fruit extracts and fractions. *BMC Complement Altern Med*., 13: 118.

Modak, M., Dixit, P., Londhe, J., Ghaskadbi, S. and Devasagayam, T. P. A. (2007). Indian herbs and herbal drugs used for the treatment of diabetes. *J Clin Biochem Nutr*., 40(3): 163-173.

Moghaddam, H. K., Baluchnejadmojarad, T., Roghani, M., Khaksari, M., Norouzi, P., Ahooie, M. and Mahboobi F. (2014). Berberine ameliorate oxidative stress and astrogliosis in the hippocampus of STZ-induced diabetic rats. *Mol Neurobiol*., 49(2): 820-6.

Mohd, K. S., Rosli, A. S., Azemin, A., Mat, N. and Zakaria, A. J. (2016). Comprehensive biological activities evaluation and quantification of marker compounds of *Ficus deltoiea* Jack varieties. *International Journal of Pharmacognosy and Phytochemical Research*, 8(10): 1698-1708.

Monnier, L., Mas, E., Ginet, C., Michel, F., Villon, L., Cristol, J. P. and Colette, C. (2006). Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2 diabetes. *JAMA*, 295(14): 1681-7.

Moore, E. M., Mander, A. G., Ames, D., Kotowicz, M. A., Carne, R. P., Brodaty, H., Woodward, M., Boundy, K., Ellis, K. A., Bush, A. I., Faux, N. G., Martins, R., Szoeke, C., Rowe, C., Watters, D. A. and AIBL Investigators. (2013). Increased risk of cognitive impairment in patients with diabetes is associated with metformin. *Diabetes Care*, 36(10): 2981-7.

Morath, C., Zeier, M., Döhler, B., Schmidt, J., Nawroth, P. P., Schwenger, V. and Opelz, G. (2010). Transplantation of the type 1 diabetic patient: the long-term benefit of a functioning pancreas allograft. *CJASN*, 5: 549-552.

Moreno, P., Acitores, A., Gutiérrez-Rojas, I., Nuche-Berenguer, B., El Assar, M., Rodriguez-Mañas, L., Gomis, R., Valverde, I., Visa, M., Malaisse, W. J., Novials, A., González, N. and Villanueva-Peñacarrillo, M. L. (2011). Amylin effect in extrapancreatic tissues participating in glucose homeostasis, in normal, insulin-resistant and type 2 diabetic state. *Peptides*, 32(10): 2077-85.

Morgese, M. G., Tucci, P., Mhillaj, E., Bove, M., Schiavone, S., Trabace, L. and Cuomo, V. (2017). Lifelong nutritional omega-3 deficiency evokes depressive-like state through soluble beta amyloid. *Mol Neurobiol*., 54(3): 2079-2089.

Morita, K., Miyamoto, T., Fujita, N., Kubota, Y., Ito, K., Takubo, K., Miyamoto, K., Ninomiya, K., Suzuki, T., Iwasaki, R., Yagi, M., Takaishi, H., Toyama, Y. and Suda, T. (2007). Reactive oxygen species induce chondrocyte hypertrophy in endochondral ossification. *J Exp Med*., 204(7): 1613-23.

Morterá, P. and Herculano-Houzel, S. (2012). Age-related neuronal loss in the rat brain starts at the end of adolescence. *Front. Neuroanat*., 6: 45.

Motyl, K. and McCabe, L. R. (2009). Streptozotocin, type I diabetes severity and bone. *Biol Proced Online*., 11: 296-315.

Motyl, K. J., McCabe, L. R. and Schwartz, A. V. (2010). Bone and glucose metabolism: a two-way street. *Arch Biochem Biophys*., 503(1): 2-10.

Mount, P. F. and Power, D. A. (2006). Nitric oxide in the kidney: functions and regulation of synthesis. *Acta Physiol (Oxf)*., 187(4): 433-46.

Mousavi, S. M., Niazmand, S., Hosseini, M., Hassanzadeh, Z., Sadeghnia, H. R., Vafaee, F. and Keshavarzi, Z. (2015). Beneficial effects of *Teucrium polium* and metformin on diabetes-induced memory impairments and brain tissue oxidative damage in rats. *Int J Alzheimers Dis*., 2015: 493729.

Movasaghi, Z., Rehman, S. and ur Rehman, I. (2008). Fourier transform infrared (FT-IR) spectroscopy of biological tissues. *Applied Spectroscopy Reviews*, 43 (2): 134-179.

Mueckler, M. and Thorens, B. (2013). The SLC2 (GLUT) family of membrane transporters. *Mol Aspects Med*., 34(2-3): 121-38.

Mukherjee, R., Mareninova, O. A., Odinokova, I. V., Huang, W., Murphy, J., Chvanov, M., Javed, M. A., Wen, L., Booth, D. M., Cane, M. C., Awais, M., Gavillet, B., Pruss, R. M., Schaller, S., Molkentin, J. D., Tepikin, A. V., Petersen, O. H., Pandol, S. J., Gukovsky, I., Criddle, D. N., Gukovskaya, A. S., Sutton, R. and NIHR Pancreas Biomedical Research Unit. (2016). Mechanism of mitochondrial permeability transition pore induction and damage in the pancreas: inhibition prevents acute pancreatitis by protecting production of ATP. *Gut*., 65(8): 1333-46.

Muller, H. and Rheinwein, H. (1927). Pharmacology of galegin. *Arch Exp Path Pharmacol*., 125: 212-228.

Muller, S. H., Diaz, J. H. and Kaye, A. D. (2015). Clinical applications of intravenous lipid emulsion therapy. *J Anesth*., 29(6): 920-6.

Musa, Y. (2005), Variability in morphology and agronomy of emas cotek accessions found in Kelantan and Terengganu. *Buletin Teknol Tanaman,* 2: 35-48.

Nagapan, G., Goh, Y. M., Abdul Razak, I. S., Nesaretnam, K. and Ebrahimi, M. (2013). The effects of prenatal and early postnatal tocotrienol-rich fraction supplementation on cognitive function development in male offspring rats. *BMC Neuroscience*, 14: 77.

Nagaraju, S., Bertera, S., Funair, A., Wijkstrom, M., Trucco, M., Cooper, D. K. C. and Bottino, R. (2014). Streptozotocin-associated lymphopenia in cynomolgus monkeys. *Islets*, 6(3): e944441.

Nahata, A., Patil, U. K. and Dixit, V. K. (2010). Effect of *Evolvulus alsinoides* Linn. on learning behavior and memory enhancement activity in rodents. *Phytother Res*., 24(4): 486-93.

Napoli, N., Chandran, M., Pierroz, D. D., Abrahamsen, B., Schwartz, A. V., Ferrari, S. L. and On behalf of the IOF Bone and Diabetes Working Group. (2017). Mechanisms of diabetes mellitus-induced bone fragility. *Nature Reviews Endocrinology*, 13: 208-219.

Nasir, A. F. A., Rahman, M. N. A., Mat, N. and Mamat, A. R. (2014). Automatic identification of *Ficus deltoidea* jack (Moraceae) varieties based on leaf. *Modern Applied Science*, 8: 121-131.

Nihayah, M., Yong, K. W. and Nur Faizah, A. B. (2012). Determination of mineral content in the *Ficus deltoidea* leaves. *Jurnal Sains Kesihatan Malaysia*, 10(2): 25-29.

Niimi, K., Yasui, T., Hirose, M., Hamamoto, S., Itoh, Y., Okada, A., Kubota, Y., Kojima, Y., Tozawa, K., Sasaki, S., Hayashi, Y. and Kohri, K. (2012). Mitochondrial permeability transition pore opening induces the initial process of renal calcium crystallization. *Free Radic Biol Med*., 52(7): 1207-17.

Nikonenko, N. A., Buslov, D. K., Sushko, N. I. and Zhbankov, R. G. (2002). Analysis of the structure of carbohydrates with use of the regularized deconvolution method of vibrational spectra. *BAÜ Fen Bil. Enst. Dergisi*., 4(2): 13-16.

Nirwane, A., Sridhar, V. and Majumdar, A. (2016). Neurobehavioural changes and brain oxidative stress induced by acute exposure to GSM900 mobile phone radiations in zebrafish (*Danio rerio*). *Toxicol Res*., 32(2): 123-132.

Nissen-Meyer, L. S., Jemtland, R., Gautvik, V. T., Pedersen, M. E., Paro, R., Fortunati, D., Pierroz, D. D., Stadelmann, V. A., Reppe, S., Reinholt, F. P., Del Fattore, A., Rucci, N., Teti, A., Ferrari, S. and Gautvik, K. M. (2007). Osteopenia, decreased bone formation and impaired osteoblast development in Sox4 heterozygous mice. *J Cell Sci*., 120(Pt 16): 2785-95.

Nolan, C. J., Madiraju, M. S., Delghingaro-Augusto, V., Peyot, M. L. and Prentki, M. (2006). Fatty acid signaling in the beta-cell and insulin secretion. *Diabetes*, 55: S16-23.

Norhaniza, A., Sin, C. Y., Chee, E. S., Nee, K. I. and Renxin, L. (2007). Blood glucose lowering effect of *Ficus deltoidea* aqueous extract. *Malays J Sci*., 26: 73-78.

Northrup, N. C., Rassnick, K. M., Gieger, T. L., Kosarek, C. E., McFadden, C. W. and Rosenberg, M. P. (2013). Prospective evaluation of biweekly streptozotocin in 19 dogs with insulinoma. *J Vet Intern Med*., 27(3): 483-90.

Nuñez, S. C., Roussotte, F. and Sowell, E. R. (2011). Focus on: structural and functional brain abnormalities in fetal alcohol spectrum disorders. *Alcohol Res Health*., 34(1): 121-132.

Nurdiana, S., Harita, H. and Farida Zuraina, M. Y. (2009). Effect of *Ficus deltoidea* leaves on glycolytic enzymes in liver of normal and streptozotocin-induced diabetic rats. *Natural Products: An Indian Journal*, 5(4): 162-166.

Oei, L., Rivadeneira, F., Zillikens, M. C. and Oei, E. H. (2015). Diabetes, diabetic complications, and fracture risk. *Curr Osteoporos Rep*., 13(2): 106-15.

Oh, S. R., Sul, O. J., Kim, Y. Y., Kim, H. J., Yu, R., Suh, J. H. and Choi, H. S. (2010). Saturated fatty acids enhance osteoclast survival. *J Lipid Res*., 51(5): 892-899.

Oh, Y. S. (2015). Plant-derived compounds targeting pancreatic beta cells for the treatment of diabetes. *Evidence-Based Complementary and Alternative Medicine*, 2015: 629863.

Okada, R., Yasuda, Y., Tsushita, K., Wakai, K., Hamajima, N. and Matsuo, S. (2012). Glomerular hyperfiltration in prediabetes and prehypertension. *Nephrol Dial Transplant*., 27(5): 1821-5.

Okere, B., Lucaccioni, L., Dominici, M. and Iughetti, L. (2016). Cell therapies for pancreatic beta-cell replenishment. *Ital J Pediatr*., 42: 62.

Oldknow, K. J., MacRae, V. E. and Farquharson, C. (2015). Endocrine role of bone: recent and emerging perspectives beyond osteocalcin. *J Endocrinol*., 225(1): R1-19.

Olsen, A. S., Sarras, M. P., Leontovich, A. and Intine, R. V. (2012). Heritable transmission of diabetic metabolic memory in zebrafish correlates with DNA hypomethylation and aberrant gene expression. *Diabetes*, 61(2): 485-91.

Olsen, J. A., Kenna, L. A., Spelios, M. G., Hessner, M. J. and Akirav, E. M. (2016). Circulating differentially methylated amylin DNA as a biomarker of β-cell loss in type 1 diabetes. *PLoS One*., 11(4): e0152662.

Omar, M. H., Mullen, W. and Crozier, A. (2011). Identification of proanthocyanidin dimers and trimers, flavone C-Glycosides, and antioxidants in *Ficus deltoidea* , a malaysian herbal tea. *J Agric Food Chem*., 59(4): 1363-9.

Ong, S. L., Ling, A. P. K., Poospooragi, R. and Moosa, S. (2010). Production of flavonoid compounds in cell cultures of *Ficus deltoidea* as influenced by medium composition. *Int J Med Aromatic Plants*, 1(2):62-74.

Onur, T., Wu, R., Metz, L. and Dang, A. (2014). Characterisation of osteoarthritis in a small animal model of type 2 diabetes mellitus. *Bone Joint Res*., 3(6): 203-211.

Ordóñez, P., Moreno, M., Alonso, A., Fernández, R., Díaz, F. and González, C. (2007). Insulin sensitivity in streptozotocin-induced diabetic rats treated with different doses of 17beta-oestradiol or progesterone. *Exp Physiol*., 92(1): 241-9.

Oury, F., Yadav, V. K., Wang, Y., Zhou, B., Liu, X. S., Guo, X. E., Tecott, L. H., Schutz, G., Means, A. R. and Karsenty, G. (2010). CREB mediates brain serotonin regulation of bone mass through its expression in ventromedial hypothalamic neurons. *Genes Dev*., 24(20): 2330-42.

Owens, D. R. (2013). Clinical evidence for the earlier initiation of insulin therapy in type 2 diabetes. *Diabetes Technol Ther*., 15(9): 776-85.

Oyenihi, O. R., Brooks, N. L. and Oguntibeju, O. O. (2015). Effects of kolaviron on hepatic oxidative stress in streptozotocin induced diabetes. *BMC Complement Altern Med*., 15: 236.

Ozder, A. (2014). Lipid profile abnormalities seen in T2DM patients in primary healthcare in Turkey: a cross-sectional study. *Lipids Health Dis*., 13: 183.

Pagliuca, F. W., Millman, J. R., Gürtler, M., Segel, M., Van Dervort, A., Ryu, J. H., Peterson, Q. P., Greiner, D. and Melton, D. A. (2014). Generation of functional human pancreatic β cells *in vitro*. *Cell*, 159(2): 428-39.

Palaniyappan, L. and Liddle, P. F. (2012). Aberrant cortical gyrification in schizophrenia: a surface-based morphometry study. *J Psychiatry Neurosci*., 37(6): 399-406.

Palatini, P. (2012). Glomerular hyperfiltration: a marker of early renal damage in pre-diabetes and pre-hypertension. *Nephrol Dial Transplant*., 27(5): 1708-14.

Palomba, L., Cerioni, L. and Cantoni, O. (2009). Arachidonic acid: a key molecule for astrocyte survival to peroxynitrite. *Glia*, 57(15): 1672-9.

Pamplona, R. and Barja, G. (2011). An evolutionary comparative scan for longevity-related oxidative stress resistance mechanisms in homeotherms. *Biogerontology*, 12(5): 409-35.

Pan, Y., Wang, Y., Cai, L., Cai, Y., Hu, J., Yu, C., Li, J., Feng, Z., Yang, S., Li, X. and Liang, G. (2012). Inhibition of high glucose-induced inflammatory response and macrophage infiltration by a novel curcumin derivative prevents renal injury in diabetic rats. *Br J Pharmacol*., 166(3): 1169-82.

Pandey, G., Shankar, K., Makhija, E., Gaikwad, A., Ecelbarger, C., Mandhani, A., Srivastava, A. and Tiwari, S. (2017). Reduced insulin receptor expression enhances proximal tubule gluconeogenesis. *J Cell Biochem*., 118(2): 276-285.

Pandya, V., Rao, A. and Chaudhary, K. (2015). Lipid abnormalities in kidney disease and management strategies. *World J Nephrol*., 4(1): 83-91.

Paneni, F., Beckman, J. A., Creager, M. A. and Cosentino, F. (2013). Diabetes and vascular disease: pathophysiology, clinical consequences, and medical therapy: part I. *Eur Heart J*., 34(31): 2436-43.

Patade, G. R. and Marita, A. R. (2014). Metformin: a Journey from countryside to the bedside. *J Obes Metab Res*., 1: 127-30.

Patel, D. K., Prasad, S. K., Kumar, R. and Hemalatha, S. (2012). An overview on antidiabetic medicinal plants having insulin mimetic property. *Asian Pac J Trop Biomed*., 2(4): 320-30.

Patwardhan, B., Warude, D., Pushpangadan, P. and Bhatt, N. (2005). Ayurveda and traditional chinese medicine: a comparative overview. *Evid Based Complement Alternat Med*., 2(4): 465-473.

Pecoits-Filho, R., Abensur, H., Betônico, C. C., Machado, A. D., Parente, E. B., Queiroz, M., Salles, J. E., Titan, S. and Vencio, S. (2016). Interactions between kidney disease and diabetes: dangerous liaisons. *Diabetol Metab Syndr*., 8: 50.

Peng, J., Hui, K., Hao, C., Peng, Z., Gao, Q. X., Jin, Q., Lei, G., Min, J., Qi, Z., Bo, C., Dong, Q. N., Bing, Z. H., Jia, X. Y. and Fu, D. L. (2016). Low bone turnover and reduced angiogenesis in streptozotocin-induced osteoporotic mice. *Connect Tissue Res*., 57(4): 277-89.

Permuy, M., Guede, D., López-Peña, M., Muñoz, F., Caeiro, J. R. and González-Cantalapiedra, A. (2015). Effects of diacerein on cartilage and subchondral bone in early stages of osteoarthritis in a rabbit model. *BMC Vet Res*., 11: 143.

Pernicova, I. and Korbonits, M. (2014). Metformin-mode of action and clinical implications for diabetes and cancer. *Nature Reviews Endocrinology*, 10: 143-156.

Petibois, C., Déléris, G., Piccinini, M., Cestelli-Guidi, M. and Marcelli, A. (2009). A bright future for synchrotron imaging. *Nature Photonics*, 3: 179.

Petibois, C., Melin, A. M., Perromat, A., Cazorla, G. and Déléris, G. (2000). Glucose and lactate concentration determination on single microsamples by Fourier-transform infrared spectroscopy. *J Lab Clin Med*., 135(2): 210-5.

Petibois, C., Rigalleau, V., Melin, A. M., Perromat, A., Cazorla, G., Gin, H. and Déléris, G. (1999). Determination of glucose in dried serum samples by Fourier-transform infrared spectroscopy. *Clin Chem*., 45(9): 1530-5.

Pezzaniti, J. L., Jeng, T. W., McDowell, L. and Oosta, G. M. (2001). Preliminary investigation of near-infrared spectroscopic measurements of urea, creatinine, glucose, protein, and ketone in urine. *Clin Biochem*., 34(3): 239-46.

Pilkington, E. H., Gurzov, E. N., Kakinen, A., Litwak, S. A., Stanley, W. J., Davis, T. P. and Ke, P. C. (2016). Pancreatic β-Cell membrane fluidity and toxicity induced by human islet amyloid polypeptide species. *Sci Rep*., 6: 21274.

Pillay, K. and Govender, P. (2013). Amylin uncovered: a review on the polypeptide responsible for type II diabetes. *BioMed Research International*, 2013: 826706.

Pimson, C., Chatuphonprasert, W. and Jarukamjorn, K. (2014). Improvement of antioxidant balance in diabetes mellitus type 1 mice by glutathione supplement. *Pak J Pharm Sci*., 27(6): 1731-7.

Pinhas-Hamiel, O. and Zeitler, P. (2005). The global spread of type 2 diabetes mellitus in children and adolescents. *J Pediatr*., 146(5): 693-700.

Piras, S., Furfaro, A. L., Domenicotti, C., Traverso, N., Marinari, U. M., Pronzato, M. A. and Nitti, M. (2016). RAGE expression and ROS generation in neurons: differentiation versus damage. *Oxid Med Cell Longev*., 2016: 9348651.

Pithadia, A., Brender, J. R., Fierke, C. A. and Ramamoorthy, A. (2016). Inhibition of IAPP aggregation and toxicity by natural products and derivatives. *Journal of Diabetes Research*, 2016: 2046327.

Pittas, A. G., Harris, S. S., Eliades, M., Stark, P. and Dawson-Hughes, B. (2009). Association between serum osteocalcin and markers of metabolic phenotype. *J Clin Endocrinol Metab*., 94(3): 827-32.

Piwkowska, A., Rogacka, D., Kasztan, M., Angielski, S. and Jankowski, M. (2013). Insulin increases glomerular filtration barrier permeability through dimerization of protein kinase G type Iα subunits. *Biochim Biophys Acta*., 1832(6): 791-804.

Podell, B. K., Ackart, D. F., Richardson, M. A., DiLisio, J. E., Pulford, B. and Basaraba, R. J. (2017). A model of type 2 diabetes in the guinea pig using sequential diet-induced glucose intolerance and streptozotocin treatment. *Dis Model Mech*., 10(2): 151-162.

Podestà, M. A., Faravelli, I., Cucchiari, D., Reggiani, F., Oldani, S., Fedeli, C. and Graziani, G. (2015). Neurological counterparts of hyponatremia: pathological mechanisms and clinical manifestations. *Curr Neurol Neurosci Rep*., 15(4): 18.

Poljsak, B., Šuput, D. and Milisav, I. (2013). Achieving the balance between ROS and antioxidants: when to use the synthetic antioxidants. *Oxidative Medicine and Cellular Longevity*, 2013: 956792.

Porat, S., Weinberg-Corem, N., Tornovsky-Babaey, S., Schyr-Ben-Haroush, R., Hija, A., Stolovich-Rain, M., Dadon, D., Granot, Z., Ben-Hur, V., White, P., Girard, C. A., Karni, R., Kaestner, K. H., Ashcroft, F. M., Magnuson, M. A., Saada, A., Grimsby, J., Glaser, B. and Dor, Y. (2011). Control of pancreatic β cell regeneration by glucose metabolism. *Cell Metab*., 13(4): 440-9.

Porter, R. L. and Calvi, L. M. (2008). Communications between bone cells and hematopoietic stem cells. *Arch Biochem Biophys*., 473(2): 193-200.

Potu, B. K., Rao, M. S., Nampurath, G. K., Chamallamudi, M. R., Nayak, S. R. and Thomas, H. (2010). Anti-osteoporotic activity of the petroleum ether extract of *Cissus quadrangularis* Linn. in ovariectomized Wistar rats. *Chang Gung Med J*., 33(3): 252-7.

Pourghasem, M., Shafi, H. and Babazadeh, Z. (2015). Histological changes of kidney in diabetic nephropathy. *Caspian J Intern Med*., 6(3): 120-127.

Prentki, M. and Nolan, C. J. (2006). Islet β cell failure in type 2 diabetes. *J Clin Invest*., 116(7): 1802-1812.

Price, D. J. (2004). Lipids make smooth brains gyrate. *Trends Neurosci*., 27(7): 362-4.

Protti, A., Lecchi, A., Fortunato, F., Artoni, A., Greppi, N., Vecchio, S., Fagiolari, G., Moggio, M., Comi, G. P., Mistraletti G., Lanticina, B., Faraldi, L. and Gattinoni, L: (2012). Metformin overdose causes platelet mitochondrial dysfunction in humans. *Crit Care*.; 16(5): R180.

Puig, J., Blasco, G., Daunis-i-Estadella, J., Moreno, M., Molina, X., Alberich-Bayarri, A., Xifra, G., Pedraza, S., Ricart, W., Fernández-Aranda, F. and Fernández-Real, J. M. (2016). Lower serum osteocalcin concentrations are associated with brain microstructural changes and worse cognitive performance. *Clin Endocrinol (Oxf)*., 84(5): 756-63.

Pushpakumar, S., Kundu, S., Narayanan, N. and Sen, U. (2015). DNA hypermethylation in hyperhomocysteinemia contributes to abnormal extracellular matrix metabolism in the kidney. *FASEB J*., 29(11): 4713-25.

Qin, S., Wen, J., Bai, X. C., Chen, T. Y., Zheng, R. C., Zhou, G. B., Ma, J., Feng, J. Y., Zhong, B. L. and Li, Y. M. (2014). Endogenous n-3 polyunsaturated fatty acids protect against imiquimod-induced psoriasis-like inflammation via the IL-17/IL-23 axis. *Mol Med Rep*., 9(6): 2097-104.

Qiu, C., Sigurdsson, S., Zhang, Q., Jonsdottir, M. K., Kjartansson, O., Eiriksdottir, G., Garcia, M. E., Harris, T. B., van Buchem, M. A., Gudnason, V. and Launer, L. J. (2014). Diabetes, markers of brain pathology and cognitive function: the Age, Gene/Environment Susceptibility-Reykjavik Study. *Ann Neurol*., 75(1): 138-46.

Qiu, W. Q., Au, R., Zhu, H., Wallack, M., Liebson, E., Li, H., Rosenzweig, J., Mwamburi, M. and Stern, R. A. (2014). Positive association between plasma amylin and cognition in a homebound elderly population. *J Alzheimers Dis*., 42(2): 555-63.

Qu, Z., Jiao, Z., Sun, X., Zhao, Y., Ren, J. and Xu, G. (2011). Effects of streptozotocin-induced diabetes on tau phosphorylation in the rat brain. *Brain Res*., 1383: 300-6.

Quesada, I., Tudurí, E., Ripoll, C. and Nadal, A. (2008). Physiology of the pancreatic alpha-cell and glucagon secretion: role in glucose homeostasis and diabetes. *J Endocrinol*., 199(1): 5-19.

Rabiei, Z., Rafieian-Kopaei, M., Heidarian, E., Saghaei, E. and Mokhtari, S. (2014). Effects of *Zizyphus jujube* extract on memory and learning impairment induced by bilateral electric lesions of the nucleus Basalis of Meynert in rat. *Neurochem Res*., 39(2): 353-60.

Rabkin, R., Ryan, M. P. and Duckworth, W. C. (1984). The renal metabolism of insulin. *Diabetologia*, 27(3): 351-7.

Ramkissoon, J. S., Mahomoodally, M. F., Subratty, A. H. and Ahmed, N. (2016). Inhibition of glucose- and fructose-mediated protein glycation by infusions and ethanolic extracts of ten culinary herbs and spices. *Asian Pacific Journal of Tropical Biomedicine*, 6(6): 492-500.

Ran, J., Ma, J., Liu, Y., Tan, R., Liu, H. and Lao, G. (2014). Low protein diet inhibits uric acid synthesis and attenuates renal damage in streptozotocin-induced diabetic rats. *J Diabetes Res*., 2014: 287536.

Ransomea, M. I. and Hannana, A. J. (2012). Behavioural state differentially engages septohippocampal cholinergic and GABAergic neurons in R6/1 Huntington's disease mice. *Neurobiology of Learning and Memory*, 97(2): 261-270.

Rao Sirasanagandla, S., Ranganath Pai Karkala, S., Potu, B. K. and Bhat, K. M. (2014). Beneficial effect of *Cissus quadrangularis* Linn. on osteopenia associated with streptozotocin-induced type 1 diabetes mellitus in male wistar rats. *Adv Pharmacol Sc*i., 2014: 483051.

Rao, V. K., Carlson, E. A. and Yan, S. S. (2014). Mitochondrial permeability transition pore is a potential drug target for neurodegeneration. *Biochim Biophys Acta*., 1842(8): 1267-72.

Raza, H. and John, A. (2012). Streptozotocin-induced cytotoxicity, oxidative stress and mitochondrial dysfunction in human hepatoma HepG2 cells. *Int J Mol Sci*., 13(5): 5751-67.

Reddy, M. A. and Natarajan, R. (2011). Epigenetics in diabetic kidney disease. J*ASN*, 22: 2182-2185.

Reddy, M. A. and Natarajan, R. (2015). Recent developments in epigenetics of acute and chronic kidney diseases. *Kidney International*, 88: 250-261.

Redfield, R. R., Scalea, J. R. and Odorico, J. S. (2015). Simultaneous pancreas and kidney transplantation: current trends and future directions. *Curr Opin Organ Transplant*., 20(1): 94-102.

Rehman, K. and Akash, M. S. H. (2016). Mechanisms of inflammatory responses and development of insulin resistance: how are they interlinked? *J Biomed Sci*., 23: 87.

Rein, M. J., Renouf, M., Cruz-Hernandez, C., Actis-Goretta, L., Thakkar, S. K. and da Silva Pinto, M. (2013). Bioavailability of bioactive food compounds: a challenging journey to bioefficacy. *Br J Clin Pharmacol*., 75(3): 588-602.

Reni, C., Mangialardi, G., Meloni, M. and Madeddu, P. (2016). Diabetes Stimulates osteoclastogenesis by acidosis-induced activation of transient receptor potential cation channels. *Scientific Reports*, 6: 30639.

Réus, G. Z., Dos Santos, M. A., Abelaira, H. M., Titus, S. E., Carlessi, A. S., Matias, B. I., Bruchchen, L., Florentino, D., Vieira, A., Petronilho, F., Ceretta, L. B., Zugno, A. I. and Quevedo, J. (2016). Antioxidant treatment ameliorates experimental diabetes-induced depressive-like behavior and reduces oxidative stress in brain and pancreas. *Diabetes Metab Res Rev*., 32(3): 278-88.

Ricksten, S. E., Bragadottir, G. and Redfors, B. (2013). Renal oxygenation in clinical acute kidney injury. *Crit Care*., 17(2): 221.

Riddle, R. C. and Clemens, T. L. (2014). Insulin, osteoblasts, and energy metabolism: why bone counts calories. *J Clin Invest*., 124(4): 1465-7.

Rigalleau, V., Lasseur, C., Perlemoine, C., Barthe, N., Raffaitin, C., Liu, C., Chauveau, P., Baillet-Blanco, L., Beauvieux, M. C., Combe, C. and Gin, H. (2005). Estimation of glomerular filtration rate in diabetic subjects: Cockcroft formula or modification of diet in renal disease study equation? *Diabetes Care*, 28(4): 838-43.

Rios-Arce, N. D., Mohr, S., Coughlin, B. A., Feenstra, D., Christian, B., McCabe, L. R. and Parameswaran, N. (2017). Interleukin-10 in type 1 diabetes-induced bone loss in mice. *The FASEB Journal*, 31: 694.10

Röder, P. V., Wu, B., Liu, Y. and Han, W. (2016). Pancreatic regulation of glucose homeostasis. *Exp Mol Med*., 48(3): e219.

Rodrigo, R. and Bosco, C. (2006). Oxidative stress and protective effects of polyphenols: Comparative studies in human and rodent kidney. *A review. Comparative Biochemistry and Physiology Part C: Toxicology & Pharmacology*, 142(3-4): 317-327.

Roep, B. O. (2013). β-Cells, autoimmunity, and the innate immune system: "un ménage á trois"? *Diabetes*, 62(6): 1821-2.

Roh, E., Song, D. K. and Kim, M. S. (2016). Emerging role of the brain in the homeostatic regulation of energy and glucose metabolism. *Exp Mol Med*., 48: e216.

Rojas, L. B. and Gomes, M. B. (2013). Metformin: an old but still the best treatment for type 2 diabetes. *Diabetol Metab Syndr*., 5(1): 6.

Roriz-Filho, J., Sá-Roriz, T. M., Rosset, I., Camozzato, A. L., Santos, A. C., Chaves, M. L., Moriguti, J. C. and Roriz-Cruz, M. (2009). (Pre)diabetes, brain aging, and cognition. *Biochim Biophys Acta*., 1792(5): 432-43.

Rosario, W., Singh, I., Wautlet, A., Patterson, C., Flak, J., Becker, T. C., Ali, A., Tamarina, N., Philipson, L. H., Enquist, L. W., Myers, M. G. Jr. and Rhodes, C. J. (2016). The brain-to-pancreatic islet neuronal map reveals differential glucose regulation from distinct hypothalamic regions. *Diabetes*, 65(9): 2711-23.

Rossini, A. A. and Soeldner, J. S. (1979). Insulin release is glucose anomeric specific in the human. *J Clin Invest*., 57(4): 1083-8.

Roza, A. M., Pieper, G. M., Johnson, C. P. and Adams, M. B. (1995). Pancreatic antioxidant enzyme activity in normoglycemic diabetic prone BB rats. *Pancreas*, 10(1): 53-8.

Rubenstein, A. H. and Spitz, I. (1968). Role of the kidney in insulin metabolism and excretion. *Diabetes*, 17(3): 161-9.

Rutebemberwa, E., Lubega, M., Katureebe, S. K., Oundo, A., Kiweewa, F. and Mukanga, D. (2013). Use of traditional medicine for the treatment of diabetes in Eastern Uganda: a qualitative exploration of reasons for choice. *BMC Int Health Hum Rights*, 13: 1.

Ryu, T. Y., Park, J. and Scherer, P. E. (2014). Hyperglycemia as a risk factor for cancer progression. *Diabetes Metab J*., 38(5): 330-336.

Saeed, M. K., Ahmad, R., Javed, S., Deng, Y. and Dai, R. (2013). Hypoglycemic and hypolipidemic effects of *Cephalotaxus sinensis* in STZ-induced diabetic rats. *Journal of Medicinal Plants Research,* 7(19): 1310-1316.

Safi, S. Z., Qvist, R., Kumar, S., Batumalaie, K. and Ismail, I. S. (2014). Molecular mechanisms of diabetic retinopathy, general preventive strategies, and novel therapeutic targets. *BioMed Research International*, 2014: 801269.

Saito, S., Teshima, Y., Fukui, A., Kondo, H., Nishio, S., Nakagawa, M., Saikawa, T. and Takahashi, N. (2014). Glucose fluctuations increase the incidence of atrial fibrillation in diabetic rats. *Cardiovasc Res*., 104(1): 5-14.

Sakata, N., Yoshimatsu, G., Tsuchiya, H., Egawa, S. and Unno, M. (2012). Animal models of diabetes mellitus for islet transplantation. *Exp Diabetes Res*., 2012: 256707.

Salleh, N. and Ahmad, V. N. (2013). *In-vitro* effect of *Ficus deltoidea* on the contraction of isolated rat's uteri is mediated via multiple receptors binding and is dependent on extracellular calcium. *BMC Complement Altern Med*., 13: 359.

Samaras, K., Lutgers, H. L., Kochan, N. A., Crawford, J. D., Campbell, L. V., Wen, W., Slavin, M. J., Baune, B. T., Lipnicki, D. M., Brodaty, H., Trollor, J. N. and Sachdev, P. S. (2014). The impact of glucose disorders on cognition and brain volumes in the elderly: the Sydney memory and ageing study. *Age (Dordr).,* 36(2): 977-93.

Sánchez-Lozada, L. G., Tapia, E., Bautista-García, P., Soto, V., Avila-Casado, C., Vega-Campos, I. P., Nakagawa, T., Zhao, L., Franco, M. and Johnson, R. J. (2008). Effects of febuxostat on metabolic and renal alterations in rats with fructose-induced metabolic syndrome. *Am J Physiol Renal Physiol*., 294(4): F710-8.

Sasidharan, S., Chen, Y., Saravanan, D., Sundram, K. M. and Latha, L Y. (2010). Extraction, isolation and characterization of bioactive compounds from plants' extracts. *Afr J Tradit Complement Altern Med*., 8(1): 1-10.

Sasson, A. N. and Cherney, D. Z. (2012). Renal hyperfiltration related to diabetes mellitus and obesity in human disease. *World J Diabetes*, 3(1): 1-6.

Sata, T. (1944). A monographic study of the genus Ficus from the point of view of economic botany. *Contr Hort Inst Taihoku Imp Univ*., 32: 1-405.

Satoh, M., Kobayashi, S., Kuwabara, A., Tomita, N., Sasaki, T. and Kashihara, N. (2010). *In vivo* visualization of glomerular microcirculation and hyperfiltration in streptozotocin-induced diabetic rats. *Microcirculation*, 17(2): 103-12.

Sayyed, S. G., Gaikwad, A. B., Lichtnekert, J., Kulkarni, O., Eulberg, D., Klussmann, S., Tikoo, K. and Anders, H. J. (2010). Progressive glomerulosclerosis in type 2 diabetes is associated with renal histone H3K9 and H3K23 acetylation, H3K4 dimethylation and phosphorylation at serine 10. *Nephrol Dial Transplant*., 25(6): 1811-7.

Schaffler, M. B., Cheung, W. Y., Majeska, R. and Kennedy, O. (2014). Osteocytes: master orchestrators of bone. *Calcif Tissue Int*., 94(1): 5-24.

Schiffrin, E. L., Lipman, M. L. and Mann, J. F. (2007). Chronic kidney disease: effects on the cardiovascular system. *Circulation*, 116(1): 85-97.

Schwartz, G. J., Muñoz, A., Schneider, M. F., Mak, R. H., Kaskel, F., Warady, B. A. and Furth, S. L. (2009). New equations to estimate GFR in children with CKD. *J Am Soc Nephrol*., 20(3): 629-37.

Schwartz, M. W., Seeley, R. J., Tschöp, M. H., Woods, S. C., Morton, G. J., Myers, M. G. and D'Alessio, D. (2013). Cooperation between brain and islet in glucose homeostasis and diabetes. *Nature*, 503(7474): 59-66.

Schwartz, S. S., Epstein, S., Corkey, B. E., Grant, S. F., Gavin, J. R. and Aguilar, R. B. (2016). The time is right for a new classification system for diabetes: rationale and implications of the β-cell-centric classification schema. *Diabetes Care*, 39(2): 179-86.

Segura, B., Baggio, H. C., Marti, M. J., Valldeoriola, F., Compta, Y., Garcia-Diaz, A. I., Vendrell, P., Bargallo, N., Tolosa, E. and Junque, C. (2014). Cortical thinning associated with mild cognitive impairment in Parkinson's disease. *Mov Disord*., 29(12): 1495-503.

Shao, J., Wang, Z., Yang, T., Ying, H., Zhang, Y. and Liu, S. (2015). Bone regulates glucose metabolism as an endocrine organ through osteocalcin. *International Journal of Endocrinology*, 2015: 967673.

Sharifzadeh, M., Ranjbar, A., Hosseini, A. and Khanavi, M. (2017). The effect of green tea extract on oxidative stress and spatial learning in streptozotocin-diabetic rats. *Iran J Pharm Res*., 16(1): 201-209.

Sharma, R. B. and Alonso, L. C. (2014). Lipotoxicity in the pancreatic beta cell: not just survival and function, but proliferation as well? *Curr Diab Rep*., 14(6): 492.

Shaw, R. A., Low-Ying, S., Leroux, M. and Mantsch, H. H. (2000). Toward reagent-free clinical analysis: quantitation of urine urea, creatinine, and total protein from the mid-infrared spectra of dried urine films. *Clinical Chemistry*, 46: 1493-1495.

Shawa, D., Graemeb, L., Pierrec, D., Elizabethd, W. and Kelvin, C. (2012). Pharmacovigilance of herbal medicine. *Journal of Ethnopharmacology*, 140(3): 513-518.

Shen, Y. C., Davies, A. G., Linfield, E. H., Taday, P. F., Arnone, D. D. and Elsey, T. S. (2003). Determination of glucose concentration in whole blood using Fourier-transform infrared spectroscopy. *J Biol Phys*., 29(2-3): 129-133.

Shetti, S., Kumar, C. D., Sriwastava, N. K. and Sharma, I. P. (2011). Pharmacovigilance of herbal medicines: current state and future directions. *Pharmacogn Mag*., 7(25): 69-73.

Shi, J., Dong, B., Mao, Y., Guan, W., Cao, J., Zhu, R. and Wang, S. (2016). Review: traumatic brain injury and hyperglycemia, a potentially modifiable risk factor. *Oncotarget*., 7(43): 71052-71061.

Shigihara, N., Fukunaka, A., Hara, A., Komiya, K., Honda, A., Uchida, T., Abe, H., Toyofuku, Y., Tamaki, M., Ogihara, T., Miyatsuka, T., Hiddinga, H. J., Sakagashira, S., Koike, M., Uchiyama, Y., Yoshimori, T., Eberhardt, N. L., Fujitani, Y. and Watada, H. (2014). Human IAPP-induced pancreatic β cell toxicity and its regulation by autophagy. *J Clin Invest*., 124(8): 3634-44.

Shimura, T., Miura, T., Usami, M., Ishihara, E., Tanigawa, K., Ishida, H. and Seino, Y. (1997). Docosahexanoic acid (DHA) improved glucose and lipid metabolism in KK-Ay mice with genetic non-insulin-dependent diabetes mellitus (NIDDM). *Biol Pharm Bull*., 20(5): 507-10.

Shum, L. C, White, N. S., Nadtochiy, S. M., Bentley, K. L., Brookes, P. S., Jonason, J. H. and Eliseev, R. A. (2016). Cyclophilin d knock-out mice show enhanced resistance to osteoporosis and to metabolic changes observed in aging bone. *PLoS One*., 11(5): e0155709.

Si, X., Li, P., Zhang, Y., Zhang, Y., Lv, W. and Qi, D. (2014). Renoprotective effects of *Olmesartan medoxomil* on diabetic nephropathy in streptozotocin-induced diabetes in rats. *Biomed Rep*., 2(1): 24-28.

Silva, J. F., Cyrino, F. Z., Breitenbach, M. M., Bouskela, E. and Carvalho, J. J. (2011). Vimentin and laminin are altered on cheek pouch microvessels of streptozotocin-induced diabetic hamsters. *Clinics (Sao Paulo)*., 66(11): 1961-8.

Silva, M. J., Brodt, M. D., Lynch, M. A., McKenzie, J. A., Tanouye, K. M., Nyman, J. S. and Wang, X. (2009). Type 1 diabetes in young rats leads to progressive trabecular bone loss, cessation of cortical bone growth, and diminished whole bone strength and fatigue life. *J Bone Miner Res*., 24(9): 1618-27.

Singh, A., Ramnath, R. D., Foster, R. R., Wylie, E. C., Fridén, V., Dasgupta, I., Haraldsson, B., Welsh, G. I., Mathieson, P. W. and Satchell, S. C. (2013). Reactive oxygen species modulate the barrier function of the human glomerular endothelial glycocalyx. *PLoS One*., 8(2): e55852.

Singh, V. P., Bali, A., Singh, N. and Jagg, A. S. (2014). Advanced glycation end products and diabetic complications. *Korean J Physiol Pharmacol*., 18(1): 1-14.

Sinha, K., Das, J., Pal, P. B. and Sil, P. C. (2013). Oxidative stress: the mitochondria-dependent and mitochondria-independent pathways of apoptosis. *Arch Toxicol*., 87(7): 1157-80.

Smith, B. C. and Denu, J. M. (2009). Chemical mechanisms of histone lysine and arginine modifications. *Biochim Biophys Acta*., 1789(1): 45-57.

Smith, Q. R. and Nagura, H. (2001). Fatty acid uptake and incorporation in brain: studies with the perfusion model. *J Mol Neurosci*., 16(2-3): 167-72.

Soltani, N., Qiu, H., Aleksic, M., Glinka, Y., Zhao, F., Liu, R., Li, Y., Zhang, N., Chakrabarti, R., Ng, T., Jin, T., Zhang, H., Lu, W. Y., Feng, Z. P., Prud'homme, G. J. and Wang, Q. (2011). GABA exerts protective and regenerative effects on islet beta cells and reverses diabetes. *Proc Natl Acad Sci U S A*., 108(28): 11692-7.

Song, J. H., Fujimoto, K. and Miyazawa, T. (2000). Polyunsaturated (n-3) fatty acids susceptible to peroxidation are increased in plasma and tissue lipids of rats fed docosahexaenoic acid-containing oils. *J Nutr*., 130(12): 3028-33.

Song, S., Zhai, Y., Li, C., Yu, Q., Lu, Y., Zhang, Y., Hua, W., Wang, Z. and Shanga, P. (2016). Effects of total flavonoids from *Drynariae Rhizoma* prevent bone loss *in vivo* and *in vitro. Bone Reports*, 5: 262-273.

Soumyanath, A., Zhong, Y. P., Henson, E., Wadsworth, T., Bishop, J., Gold, B. G., Quinn, J. F. (2012). *Centella asiatica* extract improves behavioral deficits in a mouse model of alzheimer's disease: investigation of a possible mechanism of action. *Int J Alzheimers Dis*., 2012: 381974.

Sperling, M. A. (2008). *Pediatric Endocrinology*, 3rd edition. Elsevier Health Sciences, USA.

Srinivasan, K., Viswanad, B., Asrat, L., Kaul, C. L. and Ramarao, P. (2005). Combination of high-fat diet-fed and low-dose streptozotocin-treated rat: a model for type 2 diabetes and pharmacological screening. *Pharmacol Res*., 52(4): 313-20.

Srodulski, S., Sharma, S., Bachstetter, A. B., Brelsfoard, J. M., Pascual, C., Xie, X. S., Saatman, K. E., Van Eldik, L. J. and Despa, F. (2014). Neuroinflammation and neurologic deficits in diabetes linked to brain accumulation of amylin. *Mol Neurodegener*., 9: 30.

Starup-Linde, J. (2013). Diabetes, biochemical markers of bone turnover, diabetes control, and bone. *Front Endocrinol (Lausanne)*., 4: 21.

Strömmer, L., Wickbom, M., Wang, F., Herrington, M. K., Ostenson, C. G., Arnelo, U. and Permert, J. (2002). Early impairment of insulin secretion in rats after surgical trauma. *Eur J Endocrinol*., 147(6): 825-33.

Subash-Babu, P., Alshatwi, A. A. and Ignacimuthu, S. (2014). Beneficial antioxidative and antiperoxidative effect of Cinnamaldehyde protect streptozotocin-induced pancreatic β-cells damage in wistar rats. *Biomol Ther (Seoul)*., 22(1): 47-54.

Sudo, Y., Furutani, Y., Spudich, J. L. and Kandori, H. (2007). Early photocycle structural changes in a bacteriorhodopsin mutant engineered to transmit photosensory signals. *J Biol Chem*., 282(21): 15550-8.

Sugimoto, H., Grahovac, G., Zeisberg, M. and Kalluri, R. (2007). Renal fibrosis and glomerulosclerosis in a new mouse model of diabetic nephropathy and its regression by bone morphogenic protein-7 and advanced glycation end product inhibitors. *Diabetes*, 56(7): 825-33.

Sulaiman, M. R., Hussain, M. K., Zakaria, Z. A., Somchit, M. N., Moin, S., Mohamad, A. S. and Israf, D. A. (2008). Evaluation of the antinociceptive activity of *Ficus deltoidea* aqueous extract. *Fitoterapia*, 79(7-8): 557-61.

Suman, R. K., Mohanty, I. R., Borde, M. K., Maheshwari, U. and Deshmukh, Y. A. (2016). Development of an experimental model of diabetes co-existing with metabolic syndrome in rats. *Advances in Pharmacological Sciences*, 2016: 9463476.

Sun, G. D., Cui, W. P., Guo, Q. Y. and Miao, L. N. (2014). Histone lysine methylation in diabetic nephropathy. *Journal of Diabetes Research*, 2014: 654148.

Sun, T. and Hevner, R. F. (2014). Growth and folding of the mammalian cerebral cortex: from molecules to malformations. *Nat Rev Neurosci*., 15(4): 217-32.

Suthon, S., Jaroenporn, S., Charoenphandhu, N., Suntornsaratoon, P. and Malaivijitnond, S. (2016). Anti-osteoporotic effects of *Pueraria candollei var. mirifica* on bone mineral density and histomorphometry in estrogen-deficient rats. *J Nat Med*., 70(2): 225-33.

Synytsya, A. and Novak, M. (2014). Structural analysis of glucans. *Ann Transl Med*., 2(2): 17.

Tabatabaei, S. R. F., Ghaderi, S., Bahrami-Tapehebur, M., Farbood, Y. and Rashno, M. (2017). Aloe vera gel improves behavioral deficits and oxidative status in streptozotocin-induced diabetic rats. *Biomed Pharmacother*., 96: 279-290.

Taborsky, G. J. (2011). Islets have a lot of nerve! or do they? *Cell Metab*., 14(1): 5-6.

Tahara, A., Matsuyama-Yokono, A., Nakano, R., Someya, Y. and Shibasaki, M. (2008). Hypoglycaemic effects of antidiabetic drugs in streptozotocin-nicotinamide-induced mildly diabetic and streptozotocin-induced severely diabetic rats. *Basic Clin Pharmacol Toxicol*., 103(6): 560-8.

Takiyama, Y., Harumi, T., Watanabe, J., Fujita, Y., Honjo, J., Shimizu, N., Makino, Y. and Haneda, M. (2011). Tubular injury in a rat model of type 2 diabetes is prevented by metformin: a possible role of HIF-1α expression and oxygen metabolism. *Diabetes*, 60(3): 981-92.

Talaei, F., Van Praag, V. M., Shishavan, M. H., Landheer, S. W., Buikema, H. and Henning, R. H. (2014). Increased protein aggregation in Zucker diabetic fatty rat brain: identification of key mechanistic targets and the therapeutic application of hydrogen sulfide. *BMC Cell Biol*., 15: 1.

Tang, J. and Zhuang, S. (2015). Epigenetics in acute kidney injury. *Curr Opin Nephrol Hypertens*., 24(4): 351-8.

Tang, K. S. (2014). Protective effect of arachidonic acid and linoleic acid on 1-methyl-4-phenylpyridinium-induced toxicity in PC12 cells. *Lipids Health Dis*., 13: 197.

Tang, W. H., Stitham, J., Jin, Y., Liu, R., Lee, S. H., Du, J., Atteya, G., Gleim, S., Spollett, G., Martin, K. and Hwa, J. (2014). Aldose reductase-mediated phosphorylation of p53 leads to mitochondrial dysfunction, and damage in diabetic platelets. *Circulation*, 129: 1598-609.

Taparra, K., Tran, P. T. and Zachara, N. E. (2016). Hijacking the hexosamine biosynthetic pathway to promote emt-mediated neoplastic phenotypes. *Front Oncol*., 6: 85.

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

Tervaert, T. W., Mooyaart, A. L., Amann, K., Cohen, A. H., Cook, H. T., Drachenberg, C. B., Ferrario, F., Fogo, A. B., Haas, M., de Heer, E., Joh, K., Noël, L. H., Radhakrishnan, J., Seshan, S. V., Bajema, I. M., Bruijn, J. A. and Renal Pathology Society. (2010). Pathologic classification of diabetic nephropathy. *J Am Soc Nephrol*., 21(4): 556-63.

Tfayli, H. and Arslanian, S. (2009). Pathophysiology of type 2 diabetes mellitus in youth: the evolving chameleon. *Arq Bras Endocrinol Metabol*., 53(2): 165-74.

Thombare, K., Ntika, S., Wang, X. and Krizhanovskii, C. (2017). Long chain saturated and unsaturated fatty acids exert opposing effects on viability and function of GLP-1-producing cells: mechanisms of lipotoxicity. *PLoS One*, 12(5): e0177605.

Thomson, S. C., Kashkouli, A. and Singh, P. (2013). Glucagon-like peptide-1 receptor stimulation increases GFR and suppresses proximal reabsorption in the rat. *Am J Physiol Renal Physiol*., 304(2): F137-44.

Thomson, S. C., Rieg, T., Miracle, C., Mansoury, H., Whaley, J., Vallon, V. and Singh, P. (2012). Acute and chronic effects of SGLT2 blockade on glomerular and tubular function in the early diabetic rat. *Am J Physiol Regul Integr Comp Physiol*., 302(1): R75-83.

Thorp, A. A. and Schlaich, M. P. (2015). Relevance of sympathetic nervous system activation in obesity and metabolic syndrome. *Journal of Diabetes Research*, 2015: 341583.

Thumanu, K., Sompong, M., Phansak, P., Nontapot, K. and Buensanteai, N. (2015). Use of infrared microspectroscopy to determine leaf biochemical composition of cassava in response to Bacillus subtilis CaSUT007. *Journal of Plant Interactions*, 10(1): 270-279.

Tian, L. and Yu, X. (2015). Lipid metabolism disorders and bone dysfunction--interrelated and mutually regulated (review). *Mol Med Rep*., 12(1): 783-94.

Tiwari, S., Singh, R. S., Li, L., Tsukerman, S., Godbole, M., Pandey, G. and Ecelbarger, C. M. (2013). Deletion of the insulin receptor in the proximal tubule promotes hyperglycemia. *J Am Soc Nephrol*., 24(8): 1209-14.

Tokarz, P., Kaarniranta, K. and Blasiak, J. (2013). Role of antioxidant enzymes and small molecular weight antioxidants in the pathogenesis of age-related macular degeneration (AMD). *Biogerontology*, 14(5): 461-82.

Tomita, T. (2016). Apoptosis in pancreatic β-islet cells in type 2 diabetes. *Bosn J Basic Med Sci*., 16(3): 162-179.

Trevaskis, J. L., Lei, C., Koda, J. E., Weyer, C., Parkes, D. G. and Roth, J. D. (2010). Interaction of leptin and amylin in the long-term maintenance of weight loss in diet-induced obese rats. *Obesity (Silver Spring)*, 18(1): 21-6.

Tsimihodimos, V., Mitrogianni, Z. and Elisaf, M. (2011). Dyslipidemia associated with chronic kidney disease. *Open Cardiovasc Med J*., 5: 41-48.

Tudurí, E., Beiroa, D., Stegbauer, J., Fernø, J., López, M., Diéguez, C. and Nogueiras, R. (2016). Acute stimulation of brain mu opioid receptors inhibits glucose-stimulated insulin secretion via sympathetic innervation. *Neuropharmacology*, 110: 322-32.

Unnanuntana, A., Gladnick, B. P., Donnelly, E. and Lane, J. M. (2010). The assessment of fracture risk. *J Bone Joint Surg Am*., 92(3): 743-53.

Vallon, V. and Docherty, N. G. (2014). Intestinal regulation of urinary sodium excretion and the pathophysiology of diabetic kidney disease: a focus on glucagon-like peptide 1 and dipeptidyl peptidase 4. *Exp Physiol*., 99(9): 1140-5.

van der Kraan, P. M. and van den Berg, W. B. (2012). Chondrocyte hypertrophy and osteoarthritis: role in initiation and progression of cartilage degeneration? *Osteoarthritis Cartilage*, 20(3): 223-32.

van der Ven, N. C., Hogenelst, M. H., Tromp-Wever, A. M., Twisk, J. W., van der Ploeg, H. M., Heine, R. J. and Snoek, F. J. (2005). Short-term effects of cognitive behavioural group training (CBGT) in adult type 1 diabetes patients in prolonged poor glycaemic control. A randomized controlled trial. *Diabet Med*., 22(11): 1619-23.

van der Worp, H. B., Howells, D. W., Sena, E. S., Porritt, M. J., Rewell, S., O'Collins, V. and Macleod, M. R. (2010). Can animal models of disease reliably inform human studies? *PLoS Med*., 7(3): e1000245.

Vandal, M., White, P. J., Tremblay, C., St-Amour, I., Chevrier, G., Emond, V., Lefrançois, D., Virgili, J., Planel, E., Giguere, Y., Marette, A. and Calon, F. (2014). Insulin reverses the high-fat diet-induced increase in brain Aβ and improves memory in an animal model of Alzheimer disease. *Diabetes*, 63(12): 4291-301.

VanHook, A. M. (2013). Strong bones for a strong mind. *Science Signaling*, 6(295): ec234.

Venkatesan, S., Pugazhendy, K., Sangeetha, D., Vasantharaja, C., Prabakaran, S. and Meenambal, M. (2012). Fourier Transform Infrared (FT-IR) spectoroscopic analysis of Spirulina. *International Journal of Pharmaceutical & Biological Archives*, 3(4): 969-972.

Verbalis, J. G., Barsony, J., Sugimura, Y., Tian, Y., Adams, D. J., Carter, E. A. and Resnick, H. E. (2010). Hyponatremia-induced osteoporosis. *J Bone Miner Res*., 25(3): 554-63.

Verdelis, K., Lukashova, L., Atti, E., Mayer-Kuckuk, P., Peterson, M. G., Tetradis, S., Boskey, A. L. and van der Meulen, M. C. (2011). MicroCT morphometry analysis of mouse cancellous bone: intra- and inter-system reproducibility. *Bone*, 49(3): 580-7.

Vestergaard, P. (2007). Discrepancies in bone mineral density and fracture risk in patients with type 1 and type 2 diabetes-a meta-analysis. *Osteoporos Int*., 18(4): 427-44.

Vetere, A., Choudhary, A., Burns, S. M. and Wagner, B. K. (2014). Targeting the pancreatic β-cell to treat diabetes. *Nat Rev Drug Discov*., 13(4): 278-89.

Virtanen, J. K., Mursu, J., Voutilainen, S., Uusitupa, M. and Tuomainen, T. P. (2014). Serum omega-3 polyunsaturated fatty acids and risk of incident type 2 diabetes in men: the Kuopio ischemic heart disease risk factor study. *Diabetes Care*, 37(1): 189-96.

Vlassara, H. and Uribarri, J. (2014). Advanced glycation end products (AGE) and diabetes: cause, effect, or both? *Curr Diab Rep*., 14(1): 453.

Vorhees, C. V. and Williams, M. T. (2014). Assessing spatial learning and memory in rodents. *ILAR J*., 55(2): 310-332.

Voronina, S., Collier, D., Chvanov, M., Middlehurst, B., Beckett, A. J., Prior, I. A., Criddle, D. N., Begg, M., Mikoshiba, K., Sutton, R. and Tepikin, A. V. (2015). The role of Ca^{2+} influx in endocytic vacuole formation in pancreatic acinar cells. *Biochem J*., 465(3): 405-12.

Waasdorp, M., Duitman, J., Florquin, S. and Spek, C. A. (2016). Protease-activated receptor-1 deficiency protects against streptozotocin-induced diabetic nephropathy in mice. *Sci Rep*., 6: 33030.

Wakabayashi, S., Sakurai, T. and Kashima, I. (2004). Relationships between bone strength and bone quality: three-dimensional imaging analysis in ovariectomized mice. *Oral Radiol*., 20: 32.

Wan, C., Cao, W. and Cheng, C. (2014). Research of recognition method of discrete wavelet feature extraction and pnn classification of rats FT-IR pancreatic cancer data. *Journal of Analytical Methods in Chemistry*, 2014: 564801.

Wang, D., Liu, J., He, S., Wang, C., Chen, Y., Yang, L., Liu, F., Ren, Y., Tian, H., Yang, G., Liao, G., Li, L., Shi, M., Yuan, Y., Zhao, J., Cheng, J. and Lu, Y. (2014). Assessment of early renal damage in diabetic rhesus monkeys. *Endocrine*, 47(3): 783-92.

Wang, G., Chen, L., Pan, X., Chen, J., Wang, L., Wang, W., Cheng, R., Wu, F., Feng, X., Yu, Y., Zhang, H. T., O'Donnell, J. M. and Xu, Y. (2016). The effect of resveratrol on beta amyloid-induced memory impairment involves inhibition of phosphodiesterase-4 related signaling. *Oncotarget*., 7(14): 17380-92.

Wang, J. Q., Yin, J., Song, Y. F., Zhang, L., Ren, Y. X., Wang, D. G., Gao, L. P. and Jing, Y. H. (2014). Brain aging and AD-like pathology in streptozotocin-induced diabetic rats. *Journal of Diabetes Research*, 2014: 796840.

Wang, L., Banu, J., McMahan, C. A. and Kalu, D. N. (2001). Male rodent model of age-related bone loss in men. *Bone*, 29(2): 141-8.

Wang, T., Shi, F., Jin, Y., Jiang, W., Shen, D. and Xiao, S. (2016). Abnormal changes of brain cortical anatomy and the association with plasma microrna107 level in amnestic mild cognitive impairment. *Front Aging Neurosci*., 8: 112.

Wang, X. and Zhao, L. (2016). Calycosin ameliorates diabetes-induced cognitive impairments in rats by reducing oxidative stress via the PI3K/Akt/GSK-3β signaling pathway. *Biochem Biophys Res Commun*., 473(2): 428-34.

Wang, X. H. and Huang, W. M. (2014). Astragalus polysaccharides exert protective effects in newborn rats with bronchopulmonary dysplasia by upregulating the expression of EGFL7 in lung tissue. *Int J Mol Med*., 34(6): 1529-36.

Wang, X., Misawa, R., Zielinski, M. C., Cowen, P., Jo, J., Periwal, V., Ricordi, C., Khan, A., Szust, J., Shen, J., Millis, J. M., Witkowski, P. and Hara, M. (2013). Regional differences in islet distribution in the human pancreas-preferential beta-cell loss in the head region in patients with type 2 diabetes. *PLoS One*, 8(6): e67454.

Wang, Y. H., Liu, Y. H., He, G. R., Lv, Y. and Du, G. H. (2015). Esculin improves dyslipidemia, inflammation and renal damage in streptozotocin-induced diabetic rats. *BMC Complement Altern Med*., 15: 402.

Wang, Z. X., Lloyd, A. A., Burket, J. C., Gourion-Arsiquaud, S. and Donnelly, E. (2016). Altered distributions of bone tissue mineral and collagen properties in women with fragility fractures. *Bone*, 84: 237-244.

Wathen, C. A., Foje, N., van Avermaete, T., Miramontes, B., Chapaman, S. E., Sasser, T. A., Kannan, R., Gerstler, S. and Leevy, W. M. (2013). *In vivo* X-ray computed tomographic imaging of soft tissue with native, intravenous, or oral contrast. *Sensors (Basel)*., 13(6): 6957-80.

Watschinger, B., Hartter, E., Traindl, O., Pohanka, E., Pidlich, J. and Kovarik, J. (1992). Increased levels of plasma amylin in advanced renal failure. *Clin Nephrol*., 37(3): 131-4.

Wei, D., Li, J., Shen, M., Jia, W., Chen, N., Chen, T., Su, D., Tian, H., Zheng, S., Dai, Y. and Zhao, A. (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.

Wei, J. and Karsenty, G. (2015). An overview of the metabolic functions of osteocalcin. *Rev Endocr Metab Disord*., 6(2): 93-98.

Wei, J., Ferron, M., Clarke, C. J., Hannun, Y. A., Jiang, H., Blaner, W. S. and Karsenty, G. (2014). Bone-specific insulin resistance disrupts whole-body glucose homeostasis via decreased osteocalcin activation. *J Clin Invest*., 124(4): 1-13.

Wei, J., Hanna, T., Suda, N., Karsenty, G. and Ducy, P. (2014). Osteocalcin promotes β-cell proliferation during development and adulthood through Gprc6a. *Diabetes*, 63(3): 1021-31.

Wei, S., Zhang, M., Yu, Y., Lan, X., Yao, F., Yan, X., Chen, L. and Hatch, G. M. (2016). Berberine attenuates development of the hepatic gluconeogenesis and lipid metabolism disorder in type 2 diabetic mice and in palmitate-incubated HepG2 Cells through suppression of the HNF-4α miR122 Pathway. *PLoS One*, 11(3): e0152097.

Weitzner, D. S., Engler-Chiurazzi, E. B., Kotilinek, L. A., Ashe, K. H. and Reed, M. N. (2015). Morris water maze test: optimization for mouse strain and testing environment. *J Vis Exp*., 100: 52706.

Wen, Y., Lin, N., Yan, H. T., Luo, H., Chen, G. Y., Cui, J. F., Shi, L., Chen, T., Wang, T. and Tang, L. J. (2015). Down-regulation of renal gluconeogenesis in type II diabetic rats following Roux-en-Y gastric bypass surgery: a potential mechanism in hypoglycemic effect. *Obes Facts*., 8(2): 110-24.

Weng, J., Li, Y., Xu, W., Shi, L., Zhang, Q., Zhu, D., Hu, Y., Zhou, Z., Yan, X., Tian, H., Ran, X., Luo, Z., Xian, J., Yan, L., Li, F., Zeng, L., Chen, Y., Yang, L., Yan, S., Liu, J., Li, M., Fu, Z. and Cheng, H. (2008). Effect of intensive insulin therapy on beta-cell function and glycaemic control in patients with newly diagnosed type 2 diabetes: a multicentre randomised parallel-group trial. *Lancet*, 371(9626): 1753-60.

Wennberg, A. M., Spira, A. P., Pettigrew, C., Soldan, A., Zipunnikov, V., Rebok, G. W., Roses, A. D., Lutz, M. W., Miller, M. M., Thambisetty, M. and Albert, M. S. (2016). Blood glucose levels and cortical thinning in cognitively normal, middle-aged adults. *J Neurol Sci*., 365: 89-95.

Westwell-Roper, C., Nackiewicz, D., Dan, M. and Ehses, J. A. (2014). Toll-like receptors and NLRP3 as central regulators of pancreatic islet inflammation in type 2 diabetes. *Immunol Cell Biol*., 92(4): 314-23.

Whalley, K. (2013). Bone-to-brain signalling. *Nature Reviews Neuroscience*, 14: 741.

Wicklow, B. A., Griffith, A. T., Dumontet, J. N., Venugopal, N., Ryner, L. N. and McGavock, J. M. (2015). Pancreatic lipid content is not associated with beta cell dysfunction in youth-onset type 2 diabetes. *Can J Diabetes*., 39(5): 398-404.

Wojcik, M. H., Meenaghan, E., Lawson, E. A., Misra, M., Klibanski, A. and Miller, K. K. (2010). Reduced amylin levels are associated with low bone mineral density in women with anorexia nervosa. *Bone*, 46(3): 796-800.

Wood, P. (2012). Lipidomics of Alzheimer's disease: current status. *Alzheimers Res Ther*., 4(1): 5.

Woods, S. C. and Porte, D. (1974). Neural control of the endocrine pancreas. *Physiol Rev*., 54(3): 596-619.

World Health Organization. (2016). Global report on diabetes.

Wu, N., Shen, H., Liu, H., Wang, Y., Bai, Y. and Han, P. (2016). Acute blood glucose fluctuation enhances rat aorta endothelial cell apoptosis, oxidative stress and pro-inflammatory cytokine expression *in vivo*. *Cardiovasc Diabetol*., 15(1): 109.

Wu, X., Gu, W., Lu, H., Liu, C., Yu, B., Xu, H., Tang, Y., Li, S., Zhou, J. and Shao, C. (2016). Soluble receptor for advanced glycation end product ameliorates chronic intermittent hypoxia induced renal injury, inflammation, and apoptosis via p38/jnk signaling pathways. *Oxid Med Cell Longev*., 2016: 1015390.

Wu, Y. Y., Xiao, E. and Graves, D. T. (2015). Diabetes mellitus related bone metabolism and periodontal disease. *Int J Oral Sci*., 7(2): 63-72.

Xia, C., Zhu, L., Shao, W., Mi, S., Du, S., Ye, L., Liu, M., Pang, Y., Nong, L., Jiang, C., Zhao, H. and Qi, G. (2016). The effect of hippocampal cognitive impairment and xiap on glucose and lipids metabolism in rats. *Cell Physiol Biochem*., 38(2): 609-18.

Xiao, L., Wang, X. M., Yang, T., Xiong, Y., Zhang, Z. G., Ding, J., Xu, C. and Xiong, C. Y. (2015). Changes of serum osteocalcin, calcium, and potassium in a rat model of type 2 diabetes. *Cell Biochem Biophys*., 71(1): 437-40.

Xu, C., Zhu, S., Wu, M., Zhao, Y., Han, W. and Yu, Y. (2014). The therapeutic effect of rhMK on osteoarthritis in mice, induced by destabilization of the medial meniscus. *Biol Pharm Bull*., 37(11): 1803-10.

Xu, H., Chen, K., Jia, X., Tian, Y., Dai, Y., Li, D., Xie, J., Tao, M. and Mao, Y. (2015). Metformin use is associated with better survival of breast cancer patients with diabetes: a meta-analysis. *Oncologist*, 20(11): 1236-44.

Xu, X., Guo, L. and Tian, G. (2013). Diabetes cognitive impairments and the effect of traditional chinese herbs. *Evid Based Complement Alternat Med*., 2013: 649396.

Yagil, Y., Fadem, S. Z., Kant, K. S., Bhatt, U., Sika, M., Lewis, J. B., Negoi, D. and Collaborative Study Group. (2015). Managing hyperphosphatemia in patients with chronic kidney disease on dialysis with ferric citrate: latest evidence and clinical usefulness. *Ther Adv Chronic Dis*., 6(5): 252-63.

Yahara, Y., Takemori, H., Okada, M., Kosai, A., Yamashita, A., Kobayashi, T., Fujita, K., Itoh, Y., Nakamura, M., Fuchino, H., Kawahara, N., Fukui, N., Watanabe, A., Kimura, T. and Tsumaki, N. (2016). Pterosin B prevents chondrocyte hypertrophy and osteoarthritis in mice by inhibiting Sik3. *Nat Commun*., 7: 10959.

Yamagishi, S. and Matsui, T. (2010). Advanced glycation end products, oxidative stress and diabetic nephropathy. *Oxid Med Cell Longev*., 3(2): 101-108.

Yamaguchi, M., Hamamoto, R., Uchiyama, S., Ishiyama, K. and Hashimoto, K. (2007). Preventive effects of bee pollen *Cistus ladaniferus* extract on bone loss in streptozotocin-diabetic rats *in vivo*. *Journal of Health Science*, 53: 190-195.

Yang, Z. B., Tan, B., Li, T. B., Lou, Z., Jiang, J. L., Zhou, Y. J., Yang, J., Luo, X. J. and Peng, J. (2014). Protective effect of vitexin compound B-1 against hypoxia/reoxygenation-induced injury in differentiated PC12 cells via NADPH oxidase inhibition. *Naunyn Schmiedebergs Arch Pharmacol*., 387(9): 861-71.

Yee, C. S., Xie, L., Hatsell, S., Hum, N., Murugesh, D., Economides, A. N., Loots, G. G. and Collette, N. M. (2016). Sclerostin antibody treatment improves fracture outcomes in a type I diabetic mouse model. *Bone*, 82: 122-34.

Yeom, S. Y., Kim, G. H., Kim, C. H., Jung, H. D., Kim, S. Y., Park, J. Y., Pak, Y. K., Rhee, D. K., Kuang, S. Q., Xu, J., Han, D. J., Song, D. K., Lee, J. W., Lee, K. U. and Kim, S. W. (2006). Regulation of insulin secretion and β-cell mass by activating signal cointegrator 2. *Mol. Cell. Biol*., 26: 4553-4563.

Yoshimura, M., Ono, M., Watanabe, H., Kimura, H. and Saji, H. (2014). Feasibility of amylin imaging in pancreatic islets with β-amyloid imaging probes. *Scientific Reports*, 4: 6155.

You, H., Gao, T., Cooper, T. K., Brian Reeves, W. and Awad, A. S. (2013). Macrophages directly mediate diabetic renal injury. *Am J Physiol Renal Physiol*., 305(12): F1719-27.

Yu, H., Ge, Y., Wang, Y., Lin, C. T., Li, J., Liu, X., Zang, T., Xu, J., Liu, J., Luo, G. and Shen, J. (2007). A fused selenium-containing protein with both GPx and SOD activities. *Biochem Biophys Res Commun*., 358(3): 873-8.

Yu, L. Y. and Pei, Y. (2015). Insulin neuroprotection and the mechanisms. *Chin Med J (Engl)*., 128(7): 976-81.

Yuan, Z., Wang, M., Yan, B., Gu, P., Jiang, X., Yang, X. and Cui, D. (2012). An enriched environment improves cognitive performance in mice from the senescence-accelerated prone mouse 8 strain: role of upregulated neurotrophic factor expression in the hippocampus. *Neural Regen Res*., 7(23): 1797-804.

Zehetner, J, Danzer, C., Collins, S., Eckhardt, K., Gerber, P. A., Ballschmieter, P., Galvanovskis, J., Shimomura, K., Ashcroft, F. M., Thorens, B., Rorsman, P. and Krek, W. (2008). PVHL is a regulator of glucose metabolism and insulin secretion in pancreatic beta cells. *Genes Dev*., 22(22): 3135-46.

Zeng, S., Jiang, T., Zhou, Q. C., Yuan, L., Zhou, J. W. and Cao, D. M. (2014). Time-course changes in left ventricular myocardial deformation in STZ-induced rabbits on velocity vector imaging. *Cardiovasc Ultrasound*., 12: 17.

Zhai, L., Gu, J., Yang, D., Wang, W. and Ye, S. (2015). Metformin ameliorates podocyte damage by restoring renal tissue podocalyxin expression in type 2 diabetic rats. *Journal of Diabetes Research*, 2015: 231825.

Zhang, C., Caldwell, T. A., Mirbolooki, M. R., Duong, D., Park, E. J., Chi, N. W. and Chessler, S. D. (2016). Extracellular CADM1 interactions influence insulin secretion by rat and human islet β-cells and promote clustering of syntaxin-1. Am *J Physiol Endocrinol Metab*., 310(11): E874-85.

Zhang, E. and Wu, Y. (2014). Metabolic memory: mechanisms and implications for diabetic vasculopathies. *Sci China Life Sci*., 57(8): 845-51.

Zhang, S., Liu, J., MacGibbon, G., Dragunow, M. and Cooper, G. J. (2002). Increased expression and activation of c-Jun contributes to human amylin-induced apoptosis in pancreatic islet beta-cells. *J Mol Biol*., 324(2): 271-85.

Zhang, X. and Yang, D. (2017). Occurrence of internally ovipositing non-agaonid wasps and pollination mode of the associated agaonid wasps. *Plant Diversity*, 39: 130-134.

Zhao, L., Ni, Y., Ma, X., Zhao, A., Bao, Y., Liu, J., Chen, T., Xie, G., Panee, J., Su, M., Yu, H., Wang, C., Hu, C., Jia, W. and Jia, W. (2016). A panel of free fatty acid ratios to predict the development of metabolic abnormalities in healthy obese individuals. *Sci Rep*., 6: 28418.

Zhen, Y. F., Wang, G. D., Zhu, L. Q., Tan, S. P., Zhang, F. Y., Zhou, X. Z. and Wang, X. D. (2014). P53 dependent mitochondrial permeability transition pore opening is required for dexamethasone-induced death of osteoblasts. *J Cell Physiol*., 229(10): 1475-83.

Zheng, J., Woo, S. L., Hu, X., Botchlett, R., Chen, L., Huo, Y. and Wu, C. (2015). Metformin and metabolic diseases: a focus on hepatic aspects. *Front Med*., 9(2): 173-86.

Zheng, M., Zou, C., Li, M., Huang, G., Gao, Y. and Liu, H. (2017). Folic acid reduces Tau phosphorylation by regulating PP2A methylation in streptozotocin-induced diabetic mice. *Int J Mol Sci*., 18(4): E861.

Zheng, Z. G., Zhang, X., Zhou, Y. P., Lu, C., Thu, P. M., Qian, C., Zhang, M., Li, P., Li, H. J. and Xu, X. (2017). Anhydroicaritin, a SREBPs inhibitor, inhibits RANKL-induced osteoclastic differentiation and improves diabetic osteoporosis in STZ-induced mice. *Eur J Pharmacol*., 809: 156-162.

Zhou, J., Li, X., Liao, Y., Feng, W., Fu, C. and Guo, X. (2015). Pulsed electromagnetic fields inhibit bone loss in streptozotocin-induced diabetic rats. *Endocrine*, 49: 258.

Zhou, K., Zhou, Y., Wu, K., Tian, N., Wu, Y., Wang, Y., Chen, D., Zhou, B., Wang, X., Xu, H. and Zhang, X. (2015). Stimulation of autophagy promotes functional recovery in diabetic rats with spinal cord injury. *Scientific Reports*, 5: 17130.

Zhou, L., Xu, D. Y., Sha, W. G., Shen, L., Lu, G. Y., Yin, X. and Wang, M. J. (2015). High glucose induces renal tubular epithelial injury via Sirt1/NF-kappaB/microR-29/Keap1 signal pathway. *J Transl Med*., 13: 352.

Zhou, M., Ma, X., Li, H., Pan, X., Tang, J., Gao, Y., Hou, X., Lu, H., Bao, Y. and Jia, W. (2009). Serum osteocalcin concentrations in relation to glucose and lipid metabolism in Chinese individuals. *Eur J Endocrinol*., 161(5): 723-9.

Zhou, Y. P., Xu, L., Tang, L. J., Jiang, J. H., Shen, G. L., Yu, R. Q. and Ozaki, Y. (2007). Determination of glucose in plasma by dry film-based Fourier transformed-infrared spectroscopy coupled with boosting support vector regression. *Anal Sci*., 23(7): 793-8.

Zhu, H., Wang, X., Wallack, M., Li, H., Carreras, I., Dedeoglu, A., Hur, J. Y., Zheng, H., Li, H., Fine, R., Mwamburi, M., Sun, X., Kowall, N., Stern, R. A. and Qiu, W. Q. (2015). Intraperitoneal injection of the pancreatic peptide amylin potently reduces behavioral impairment and brain amyloid pathology in murine models of Alzheimer's disease. *Molecular Psychiatry*, 20: 252-262.

Zhu, X. H., Lu, M., Lee, B. Y., Ugurbil, K. and Chen, W. (2015). *In vivo* NAD assay reveals the intracellular NAD contents and redox state in healthy human brain and their age dependences. *Proc Natl Acad Sci U S A*., 112(9): 2876-81.

Zhukouskaya, V. V., Eller-Vainicher, C., Shepelkevich, A. P., Dydyshko, Y., Cairoli, E. and Chiodini, I. (2015). Bone health in type 1 diabetes: focus on evaluation and treatment in clinical practice. *J Endocrinol Invest*., 38(9): 941-50.

Zimisuhara, B., Valdiani, A., Shaharuddin, N. A., Qamaruzzaman, F. and Maziah, M. (2015). Structure and principal components analyses reveal an intervarietal fusion in malaysian mistletoe fig (*Ficus deltoidea* Jack) populations. *Int J Mol Sci*., 16(7): 14369-14394.

Zou, X. F., Ji, Y. T., Gao, G., Zhu, X. J., Lv, S. W., Yan, F., Han, S. P., Chen, X., Gao, C. C., Liu, J. and Luo, G. M. (2010). A novel selenium and copper-containing peptide with both superoxide dismutase and glutathione peroxidase activities. *J Microbiol Biotechnol*, 20(1): 88-93.