UNIVERSITI PUTRA MALAYSIA

ANTIDIABETIC EFFECTS OF Melicope lunu-ankenda (GAERTN.) T.G. HARTLEY ON OBESE STZ-INDUCED DIABETIC RATS USING NMR-BASED METABOLOMICS

MIZHER HEZAM BAROOR AL-ZUAIDY

FSTM 2016 26

ANTIDIABETIC EFFECTS OF *Melicope lunu-ankenda* (GAERTN.) T.G. HARTLEY ON OBESE STZ-INDUCED DIABETIC RATS USING NMR-BASED METABOLOMICS

By

MIZHER HEZAM BAROOR AL-ZUAIDY

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

December 2016

COPYRIGHT

DEDICATION

This thesis is dedicated to my parents, family, brothers, sisters and friends.

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

ANTIDIABETIC EFFECTS OF *Melicope lunu-ankenda* (GAERTN.) T.G. HARTLEY ON OBESE STZ-INDUCED DIABETIC RATS USING NMR-BASED METABOLOMICS

By

MIZHER HEZAM BAROOR AL-ZUAIDY

December 2016

Chairman : Prof. Azizah Abdul Hamid, PhD
Faculty : Food Science and Technology

In the present study, antioxidant and antidiabetic activities of different *Melicope Lunu-ankenda* (ML) ethanolic extracts were evaluated using *in vitro* and *in vivo* models. Proton nuclear magnetic resonance (^{1}H NMR) and ultra-high performance liquid chromatography tandem mass spectrometry (UHPLC-MS/MS) were used to profile the bioactive metabolites in ML leaf extracts. Sixty percent ethanolic ML extract showed the highest inhibitory effect against α-glucosidase, DPPH scavenging activity and ferric reducing antioxidant power. Results based on cell line investigations showed that the leaf extract stimulated the glucose uptake by both 3T3-L1 and HepG2 cells. A discriminatory study on the metabolites responsible for the variation between different ethanolic ML extracts was successfully performed using ^{1}H-NMR-based metabolomics. Principal component analysis (PCA) and partial least square discriminant analysis (PLS-DA) scores revealed clear and distinct separations by PC1 and PC2 with an eigenvalue of 69.9%. The main bioactive compounds found responsible for the separation were isorhamnetin, skimmianine, scopoletin and melicarpinone. The antidiabetic effect was also carried out *in vivo* using rat models. The extract exerted its effect by decreasing the blood glucose level, insulin resistance, and increasing insulin sensitivity. The treatment of obese diabetic rats with ML extract also resulted in significant decrease in TG, TC, and LDL levels. However, HDL levels were significantly increased. The impact of treatment was also observed in terms of regulation of the renal injury markers and activities of liver enzymes.

In addition, NMR-based metabolomics and multivariate data analysis showed clear metabolic differences in the serum and urine samples of healthy, diabetic and treated diabetic Sprague-dawley rats. The metabolomics results demonstrated that the observed metabolic changes were linked with diabetes progression, and metabolic biomarkers were reflected by the perturbed metabolites, hence providing clear understanding regarding the underlying mechanism involved in generation and progression of diabetes. This study presented potent antidiabetic activity of ML and

describes its mechanism of action. The NMR based metabolomics approach is supportive for the additional understanding of diabetes-related mechanisms and enhances the metabolic pathways affected in the diabetic rats. These results of the present study may further contribute towards understanding of the underlying molecular mechanism of this medicinal remedy.

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

KESAN ANTIDIABETIK *Melicope lunu-ankenda* DI DALAM TIKUS DIABETIK TERARUH STZ OBES MENGGUNAKAN METABOLOMIK BERASASKAN NMR

Oleh

MIZHER HEZAM BAROOR AL-ZUAIDY

Disember 2016

Pengerusi : Prof. Azizah Abdul Hamid, PhD
Fakulti : Sains danTeknologi Makanan

Di dalam kajian ini, aktiviti-aktiviti antioksida dan antidiabetik ekstrak-ekstrak ethanol *Melicope Lunu-ankenda* (ML) yang berbeza telah dinilai menggunakan model-model *in vitro* dan *in vivo*. Resonans magnetik nuklear proton (^{1}H NMR) dan kromatografi cecair prestasi ultra-tinggi spektrometri jisim seiring (UHPLC-MS/MS) telah digunakan untuk memprofil metabolit-metabolit bioaktif di dalam ekstrak daun ML. Ekstrak ML etanol enam puluh peratus menunjukkan kesan perencatan yang paling tinggi terhadap α-glucosidase, aktiviti memerangkap DPPH dan kuasa antioksidan penurunan ferik. Keputusan berdasarkan siasatan barisan sel menunjukkan bahawa ekstrak daun tersebut merangsang pengambilan glukosa oleh kedua-duanya sel-sel 3T3-L1 dan HepG2. Satu kajian berdiskriminasi ke atas metabolit-metabolit yang bertanggungjawab ke atas variasi di antara ekstrak-ekstrak ML etanol yang berbeza telah dilakukan dengan jayanya menggunakan metabolomik berasaskan-^{1}H-NMR. Analisis komponen utama (PCA) dan skor-skor separa kuasa dua terkecil analisis diskriminan (PLS-DA) menunjukkan pemisahan yang jelas dan berbeza oleh PC1 dan PC2 dengan nilai eigen 69.9%. Sebatian bioaktif utama yang didapati bertanggungjawab bagi pemisahan itu ialah isorhamnetin, skimmianine, scopoletin dan melicarpinone. Kesan antidiabetik turut dijalankan *in vivo* menggunakan model tikus. Ekstrak tersebut mengenakan kesannya dengan mengurangkan paras glukosa darah, rintangan insulin, dan meningkatkan sensitiviti insulin. Rawatan tikus diabetik obes dengan ekstrak ML juga menyebabkan penurunan ketara bagi paras-paras TG, TC, dan LDL. Walau bagaimanapun, paras HDL telah meningkat dengan ketara. Kesan rawatan juga diperhatikan dari segi pengawalan penanda-penanda kecederaan buah pinggang dan aktiviti enzim hati.

Di samping itu, metabolomik berasaskan-NMR dan analisis data pelbagai pembolehubah menunjukkan perbezaan metabolik yang jelas di dalam sampel-sampel serum dan air kencing tikus Sprague-Dawley sihat, berdiabetes, dan berdiabetes yang dirawat. Keputusan metabolomik menunjukkan bahawa perubahan-perubahan metabolisme yang diperhatikan adalah berkaitkan dengan perkembangan

diabetes, dan penanda-penanda biologi metabolisme digambarkan oleh metabolit-metabolit yang terganggu, justeru itu memberikan kefahaman yang jelas mengenai mekanisme asas yang terlibat dalam penjanaan dan perkembangan diabetes. Kajian ini telah membentangkan aktiviti antidiabetik ML yang kuat dan menerangkan mekanisme tindakannya. Pendekatan metabolomik berasaskan NMR menyokong pemahaman tambahan terhadap mekanisme-mekanisme yang berkaitan dengan diabetes dan meningkatkan laluan metabolik yang terlibat di dalam tikus berdiabetes. Hasil-hasil kajian ini mungkin boleh selanjutnya menyumbang ke arah pemahaman mengenai mekanisme di paras molekul bagi remedi mengubat ini.

ACKNOWLEDGEMENTS

All praise is to Almighty ALLAH (SWT) and peace is upon His messenger, prophet Mohammad (PBUH).

I appreciate and acknowledge the efforts of my humble supervisor, Prof. Dr. Azizah Abdul Hamid, for her general supervision coupled with excellent attention, patience and valuable suggestions offered throughout the course of this work.

I also want to give my warm appreciation to my committee members: Prof. Dr. Amin Ismail, Prof. Dr. Suhaila Mohamed and Dr. Ahmad Faizal Abdul Razis for their helpful suggestions, insights and comments.

I would like to thank the various members of our Research group with whom I had the opportunity to work with to mention few Dr. Muhammad Waseem Mumtaz,. They provided a friendly and cooperative atmosphere at work and also useful feedback and insightful comments on mywork.

And also the entire staffs of the Faculty of Food Science and Technology and Institute of Bioscience for their kind support and assistance towards the successful completion of this thesis.

I will like to express my profound and heartfelt gratitude to my wife, daughters, relatives, friends and all other well-wishers for their interest and immense contributions in prayers, guidance and moral support towards my success.

I certify that a Thesis Examination Committee has met on 19 December 2016 to conduct the final examination of Mizher Hezam Baroor Al-Zuaidy on his thesis entitled "Antidiabetic Effects of *Melicope lunu-ankenda* (Gaertn.) T.G. Hartley on Obese STZ-Induced Diabetic Rats using NMR-Based Metabolomics" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the Doctor of Philosophy.

Members of the Thesis Examination Committee were as follows:

Faridah binti Abas, PhD
Associate Professor
Faculty of Food Science and Technology
Universiti Putra Malaysia
(Chairman)

Son Radu, PhD
Professor
Faculty of Food Science and Technology
Universiti Putra Malaysia
(Internal Examiner)

Jinap binti Selamat, PhD
Professor
Institute of Tropical Agriculture & Food Security
Universiti Putra Malaysia
(Internal Examiner)

Farooq Anwar, PhD
Associate Professor
Prince Sattam Bin Abdulaziz University
Saudi Arabia
(External Examiner)

NOR AINI AB. SHUKOR, PhD
Professor and Deputy Dean
School of Graduate Studies
Universiti Putra Malaysia

Date: 26 January 2017

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

Azizah Abdul Hamid, PhD
Professor
Faculty of Food Science and Technology
Universiti Putra Malaysia
(Chairman)

Amin Ismail, PhD
Professor
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Member)

Suhaila Mohamed, PhD
Professor
Institute of Bioscience
Universiti Putra Malaysia
(Member)

Ahmad Faizal Abdul Razis, PhD
Associate Professor
Faculty of Food Science and Technology
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.: Mizher Hezam Baroor AL-Zuaidy, GS37688

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 University Putra Malaysia (Graduate Studies) Rules 2003 (Revision 2012-2013) are adhered to.

Signature: _____
Name of
Chairman of
Supervisory
Committee: Professor Dr. Azizah Abdul Hamid

Signature: _____
Name of
Member of
Supervisory
Committee: Professor Dr. Amin Ismail

Signature: _____
Name of
Member of
Supervisory
Committee: Professor Dr. Suhaila Mohamed

Signature: _____
Name of
Member of
Supervisory
Committee: Assoc. Prof. Dr. Ahmad Faizal Abdul Razis

TABLE OF CONTENTS

		Page
ABSTRACT		i
ABSTRAK		iii
ACKNOWLEDGEMENTS		v
APPROVAL		vi
DECLARATION		viii
LIST OF TABLES		xiv
LIST OF FIGURES		xv
LIST OF ABBREVIATIONS		xix
CHAPTER		
1	**INTRODUCTION**	1
	1.1 Background	1
	1.2 Problem Statement	3
	1.3 Hypothesis	3
	1.4 Objectives of the study	3
2	**LITERATURE REVIEW**	4
	2.1 Diabetes mellitus and public health	4
	2.2 Classification and etiology of diabetes mellitus (DM)	4
	2.2.1 Type 1 diabetes mellitus (T1DM)	4
	2.2.2 Type-2 diabetes mellitus (T2DM)	5
	2.3 Diabetes and oxidative Stress	6
	2.3.1 Source of oxidative stress in diabetes	7
	2.3.2 Biomarkers of oxidative stress relative to diabetes mellitus	8
	2.3.2.1 Proteins	8
	2.3.2.2 Lipids	8
	2.3.2.3 Vitamins	8
	2.3.2.4 Glutathione	9
	2.3.2.5 Catalase	10
	2.3.2.6 Superoxide dismutase	10
	2.4 Insulin and its function in body	11
	2.4.1 Role of insulin resistance in development of T2DM	12
	2.5 Alpha glucosidase inhibitors and diabetes mellitus	12
	2.5.1 Source and characteristics of α-glucosidase inhibitors	13
	2.3.3 Mechanism of α-glucosidase inhibitors	13
	2.4 Plant Food Supplements	14
	2.5 Melicope lunu-ankenda (ML)	14
	2.6 Treatment strategies for diabetes mellitus	16
	2.5.1 Synthetic remedies for diabetes mellitus	16
	2.6.1 Herbal remedies for diabetes mellitus	17
	2.7 Mechanism of medicinal plant action in diabetes mellitus	18
	2.8 Phytochemicals and their significance	18
	2.8.1 Bioavailability of polyphenols	20

2.9 Modelling type 2 diabetes in rats using high fat diet and streptozotocin 20
2.10 Streptozotocin (STZ) treatment make the model T2DM animal 21
2.11 Metabolomics 21
2.11.1 Metabolomics and its applications 22
2.11.2 Metabolomics and its clinical applications 23
2.11.3 Metabolomics specific to diabetes mellitus 23
2.11.4 Analytical techniques for metabolomics 25
2.11.4.1 Nuclear magnetic resonance (NMR) spectroscopy 26
2.11.4.2 Mass spectrometry (MS) 28
2.11.4.3 Gas chromatography-mass spectroscopy (GC-MS) 29
2.11.4.4 Liquid chromatography-masss pectrometry (LC-MS) 29
2.12 Chemometrics and metabolomics 30
2.12.1 Principal component analysis (PCA) 30
2.12.2 Partial least square discriminant analysis (PLS-DA) 30
2.12.3 Orthogonal projections to latent structures (OPLS) 31

3 BIOLOGICAL ACTIVITIES AND CYTOTOXICITY OF *MELICOPE LUNU-ANKENDA* LEAF EXTRACT, AN *IN VITRO* STUDY 32
3.1 Introduction 32
3.2 Methods and materials 33
3.2.1 Chemicals and reagents 33
3.2.2 Plant materials and extraction 33
3.2.3 Determination of total phenolic compounds (TPC) 34
3.2.4 Determination of total flavonoids content (TFC) 34
3.2.5 DPPH Radical scavenging activity 34
3.2.6 Ferric reducing antioxidant power (FRAP) 35
3.2.7 Inhibition of α-glucosidase activity assay 35
3.2.8 Maintenance of cell lines 36
3.2.9 Evaluation of cytotoxicity of 60% ethanolic ML extract 36
3.2.10 Glucose uptake studies of 60% ethanolic ML extract 36
3.2.11 Statistical analysis 37
3.3 Results 37
3.3.1 Percent extraction yield 37
3.3.2 Total phenolic compounds (TCP) 37
3.3.3 Total flavonoid content (TFC) 38
3.3.4 DPPH Radical scavenging activity 39
3.3.5 Ferric reducing antioxidant power 40
3.3.6 Inhibition of α-glucosidase activity 41
3.3.7 Glucose uptake study 42
3.3.8 Cytotoxicity Study 44
3.4 Discussion 45
3.5 Conclusion 48

4 ^{1}H NMR-BASED METABOLITE PROFILING OF *MELICOPE LUNU-ANKENDA* LEAF IN CORRELATION TO ITS BIOLOGICAL ACTIVITY 49

4.1 Introduction 49

4.2 Methods and materials 50

4.2.1 Chemicals and reagents 50

4.2.2 Plant materials and extraction 50

4.2.3 ^{1}H NMR Measurement and data analysis 50

4.2.4 Ultra-high performance liquid chromatography tandem mass spectrometry (UHPLC-MS/MS) method 51

4.2.5 Statistical analysis 51

4.3 Results 51

4.3.1 ^{1}H NMR Spectra and metabolites identification 51

4.3.2 UHPLC-MS/MS analysis 55

4.3.3 Multivariate analysis of ML extract 56

4.3.4 Correlation between α-glucosidase inhibition and antioxidant activity with that of metabolites in ML extract 58

4.4 Discussion 61

4.5 Conclusion 63

5 ANTIDIABETIC ACTIVITY OF *MELICOPE LUNU-ANKENDA* LEAF EXTRACT IN OBESE STZ INDUCED DIABETIC RATS 64

5.1 Introduction 64

5.2 Material and methods 64

5.2.1 Plant Materials and Extraction 64

5.2.2 Experimental Animals 65

5.2.3 Experimental Design 66

5.2.4 Food and water Consumption Measurements 67

5.2.5 Sacrifice of rats 67

5.2.6 Blood glucose level measurement 67

5.2.7 Biochemical analyses 67

5.2.8 Determination of insulin 67

5.2.9 Calculation of Insulin Resistance and insulin sensitivity 68

5.2.10 Statistical Analysis 68

5.3 Results 68

5.3.1 Induction of obesity 68

5.3.2 Effect of ML extract on the food and water consumption 69

5.3.3 Effects ml extract on the body weight changes 71

5.3.4 Effect of ML extract on blood glucose level 71

5.3.5 Effect of ML extract on fasting serum insulin 72

5.3.6 Effect of ML extract on insulin sensitivity and insulin resistance 73

5.3.7 Effects of ML extract on the serum lipid profile 75

5.3.8 Effect of ML extracts on liver enzymes activities 78

5.3.9 Effects on the serum urea and creatinine Levels 79

5.3.10 Effect of ML extract on body organs weight 81

5.4 Discussion 83

5.5 Conclusion 86

6 METABOLITES CHANGHES IN OBESE STZ INDUCED DIABETIC RATS TREATED WITH *MELICOPE LUNU-ANKENDA* USING ^{1}H-NMR BASED METABOLOMICS 87
6.1 Introduction 87
6.2 Methodology 88
6.2.1 Animal study 88
6.2.2 Serum and urine collection 88
6.2.3 ^{1}H NMR Analysis of urine and serum 88
6.2.4 ^{1}H NMR Spectral data reduction and multivariate data analysis 89
6.2.5 Statistical analysis 89
6.3 Results 89
6.3.1 ^{1}H NMR Spectra of urine metabolites before treatment 89
6.3.2 Multivariate data analysis of urine samples of obese diabetic and normal rats 92
6.3.3 Multivariate data analysis of urine NMR data of all groups at week8 of treatment 94
6.3.4 Metabolites analysis of urine NMR data of ML and metformin at different period of treatment 97
6.3.5 ^{1}H NMR Spectra of serum metabolites before treatment 100
6.3.6 Multivariate data analysis of serum samples of obese diabetic and normal rats 103
6.3.7 Multivariate data analysis of serum NMR data of all groups at week8 of treatment 105
6.3.8 Metabolites analysis of serum NMR data of ML extract and metformin at different period of treatment 110
6.4 Discussion 113
6.4.1 Metabolic alterations in urine and serum samples of obese diabetic and normal rats 113
6.4.2 Metabolic alterations of the response to ML extract treatment 115
6.4.2.1 Lipid metabolism 116
6.4.2.2 Glucose metabolism 117
6.4.2.3 Tricarboxylic acid (TCA) cycle 117
6.4.2.4 Amino acid metabolism 118
6.5 Conclusions 119

REFERENCES 122
APPENDICES 149
BIODATA OF STUDENT 155
LIST OF PUBLICATIONS 156

LIST OF TABLES

Table		Page
2.1	Botanical classification of *Melicope lunu-ankenda*	14
3.1	Percentage yield of ML extracts at different % ethanol levels	37
3.2	Effect of ML extracts on HepG2 and 3t3-L1 viability after treatment with different concentration (3.125-200 µg/mL) for 24hr, 48hr and 72hr	44
4.1	^{1}H NMR characteristics of identified metabolites in ML extract.	53
4.2	Major Identified compounds in ML Extract by UHPLC -MS/MS	55
4.3	The VIP values based on score plots of PLS model of the main compound reflecting their separation.	61
5.1	Composition of diet	65
5.2	Serum alanine aminotransferase (ALT), alkaline phosphatase (ALP) aspartate aminotransferase (AST), creatinine and urea levels at week0 and week8 of treatment in different groups	80
5.3	Weight of rat body organs liver, kidney and spleen	82
6.1	Relative quantitative of discriminating metabolites of urine in obese diabetic rats (DG) and normal diet rats (NG) before treatment	91
6.2	Relative quantitative of significant discriminating metabolites of urine at week8 of treatment	96
6.3	Relative quantitative of discriminating metabolites of serum in obese diabetic rats (DG) and normal diet rats (NG) before treatment	102
6.4	Relative quantitative of significant discriminating metabolites of blood at week8 of treatment	109

LIST OF FIGURES

Figure		Page
2.1	GSH synthesis	9
2.2	Main enzymatic antioxidant defines system *in vivo* and their reactions on scavenging free radicals and hydrogen oxide	10
2.3	*Melicope lunu-ankenda*	15
2.4	Basic chemical structure and numbering pattern of flavonoids	19
2.5	Typical procedure describing metabolite profiling based NMR	27
2.6	MS ion types usually involved in metabolite identification	28
3.1	TPC of different concentrations of ML ethanol Extraction	38
3.2	TFC of different concentrations of ML ethanol Extraction	39
3.3	DPPH scavenging activity of ethanolic ML extracts (40 %, 60 %, 80 % and 100 %)	40
3.4	FRAP value of different concentrations of ML ethanol extraction	41
3.5	Alpha-glucosidase inhibitory activity of different ethanolic ML extracts (40 %, 60 %, 80 % and 100 %)	42
3.6	Effects of different contention of ML extract on glucose uptake by HepG2	43
3.7	Effects of the crude extracts of ML on glucose uptake by 3T3-L1	44
4.1	The representative 1H-NMR spectra of the four ethanolic ML extracts (40 %, 60 %, 80 % and 100 %)	52
4.2	The representative expanded 1H NMR spectra (δ 4.5 to 8) of the four ML extracts (40 %, 60 %, 80 % and 100 %).	53
4.3	Figure 4.3. A & B- 1H–1H J-resolved spectra of 60% ML extract in the region δ 3.1 to 7.9.	54
4.4	Chemical structures of isorhamnetin; skimmianine; scopoletin; melicarpinone	54
4.5	ESI-MS/MS spectrums of A; isorhamnetin, B; skimmianine, C; scopoletin, and D; melicarpinone	55
4.6	A; the PCA score plot (PC1 vs. PC2) and B; loading scatter plot of 60 % and 80 %	57
4.7	The PLS loading column plots of 40, 60, 80 and 100 %	57

4.8	The biplot obtained from PLS describing the variation between the main bioactive compounds in the different ethanolic extract of ML and their correlation to DPPH and inhibition of α-glucosidase activity (IGA)	58
4.9	permutation test OF PLS model based on NMR data of DPPH and inhibition of α-glucosidase activity (IGA)	59
4.10	The regression coefficients of Y variables of PLS validation of DPPH and α-glucosidase inhibitory activity	60
5.1	Schematic diagram of the experimental design to evaluate the antidiabetic effect of 60% ethanolic of ML leaf extract in obese diabetic male Sprague-Dawley rats	60
5.2	Body weight gain of normal diet group (NG) and high fat diet (HFD) groups after 8 weeks of induce obesity	66
5.3	Average of food intake from the week0 to the week8 of treatment	69
5.4	Average of drinking water consumption from the week0 to the week8 of treatment	70
5.5	Body weight of normal diet group (NG), diabetic group (DG), metformin group (MG) low dose group (LDG) and high dose group (HDG) at week zero (wk0) and week eight (wk8) of treatment	70
5.6	Serum glucose level (mmol\L) of normal diet group (NG), obese diabetic group (DG), metformin group (MG) low dose group (LDG) and high dose group (HDG) at week zero (wk0) and week eight (wk8) of treatment	71
5.7	Serum insulin levels (ug\L) of normal diet group (NG), obese diabetic group (DG), metformin group (MG) low dose group (LDG) and high dose group (HDG) at week zero (wk0) and week eight (wk8) of treatment	72
5.8	Insulin sensitivity values of normal diet group (NG), diabetic group (DG), metformin group (MG) low dose group (LDG) and high dose group (HDG) at week zero (wk0) and week eight (wk8) of treatment	73
5.9	Insulin resistance values of normal diet group (NG), diabetic group (DG), metformin group (MG) low dose group (LDG) and high dose group (HDG) at week zero (wk0) and week eight (wk8) of treatment	74

5.10	Total cholesterol levels of normal diet group (NG), diabetic group (DG), metformin group (MG) low dose group (LDG) and high dose group (HDG) at week zero (wk0) and week eight (wk8) of treatment	75
5.11	Triglycerides levels of normal diet group (NG), diabetic group (DG), metformin group (MG) low dose group (LDG) and high dose group (HDG) at week zero (wk0) and week eight (wk8) of treatment	76
5.12	LDL levels of normal diet group (NG), diabetic group (DG), metformin group (MG) low dose group (LDG) and high dose group (HDG) at week zero (wk0) and week eight (wk8) of treatment	77
5.13	HDL levels of normal diet group (NG), diabetic group (DG), metformin group (MG) low dose group (LDG) and high dose group (HDG) at week zero (wk0) and week eight (wk8) of treatment	78
6.1	Typical 500 MHz 1HNMR urine A (1 to 3ppm), B (3 to 6ppm), and C (6- to 9ppm) spectra with identified metabolites collected from obese diabetes group (DG) and normal diet group (NG) Sprague Dawley rat	90
6.2	PCA score plot obtained using 1 H NMR data for urine samples from obese diabetic group (DG) and normal diet group (NG) before treatment	92
6.3	Loading plot obtained using 1 H NMR data for urine samples from obese diabetic group (DG) and normal diet group (NG)	93
6.4	PCA column plot obtained using 1 H NMR data for urine samples from obese diabetic group (DG) and normal diet group (NG)	93
6.5	PCA score plot (A) and loading plot (B) obtained using 1 H NMR data for urine samples from Sprague-Dawley at week8 of treatment	95
6.6	OPLS-DA score plots (A and B) of ML and metformin obtained using ^{1}H NMR data for urine samples from Sprague-Dawley rats, week0 (HDG0 and MG0), week4 (HDG4 and MG4) and week8 (HDG8 and MGF8)	95
6.7	loading column plot of ML obtained using 1 H NMR data for urine samples from Sprague-Dawley rats, week0 (HDG0), and week8 (HDG8)	98
6.8	Loading column plot of metformin obtained using 1 H NMR data for urine samples from Sprague-Dawley rats, week0 (MG0), and week8 (MG8	99

6.9	Typical 500 MHz 1HNMR serum (A&B) spectra collected from obese diabetes group (DG) and normal diet group (NG) Sprague Dawley rat before treatment·	101
6.10	PCA score plot (A), loading plot (B) obtained using 1 H NMR data for serum samples from Sprague-Dawley rats, obese diabetic group (DG) and normal diet group (NG) before treatment	104
6.11	PCA column plot obtained using 1 H NMR data for serum samples from Sprague-Dawley rats, obese diabetic group (DG) and a normal die (ND) before treatment	105
6.12	PCA score plot (A) and OPLS-DA score (B) obtained using 1 H NMR data for serum samples from Sprague-Dawley rats, obese diabetic group (DG), normal diet group (NG), metformin group (MG), low dose group (LDG) or high dose group (HDG) at week8 of treatment	107
6.13	PCA Loading plot obtained using 1 H NMR data for serum samples from Sprague-Dawley rats, obese diabetic group (DG), normal diet group (NG), metformin group (MG), low dose group (LDG) or high dose group (HDG) at week8 of treatment	108
6.14	OPLS-DA score plot (A and B) of ML and metformin obtained using 1 H NMR data for serum samples from Sprague-Dawley rats at week8 of treatment	111
6.15	OPLS-DA loading column plot of ML obtained using 1 H NMR data for serum samples from Sprague-Dawley rats, Week0 (HDG0), and Week8 (HDFG8)	112
6.16	OPLS-DA loading column metformin obtained using 1 H NMR data for serum samples from Sprague-Dawley rats, Week0 (MG0), and Week8 (MG8)	112
6.17	Metabolism pathways describing regulation of potential urine and serum biomarkers upon ML extract treatment	120
A1	Normal rat at week8 of treatment	149
A2	Obese diabetic rat(DG) at week8 of treatment	149
A3	Obese diabetic rat treated with metformin at week8 of treatment	150
A4	Obese diabetic rat treated with high dose of ML extract at week8 of treatment	151
A5	Obese diabetic rat treated with low dose of ML extract at week8 of treatment	152

LIST OF ABBREVIATIONS

^{1}H NMR	Proton Nuclear Magnetic Resonance Spectroscopy
d	Doublet
DPPH	Diphenyl picrylhydrazyl
ESI	Electrospray Ionization
FRAP	Ferric reducing antioxidant power
g	Gram
GAE	Gallic Acid Equivalent
gCOSY	Gradient Correlation Spectroscopy
gHMBC	Gradient Heteronuclear Multiple Bond Correlation
gHSQC	Gradient Heteronuclear Single-Quantum Coherence
Hz	Hertz
hr	hour
IC_{50}	Inhibition Concentration at 50 percent
IR	Infra-red
L	Litre
LC-MS	Liquid Chromatography–Mass Spectrometry
m	Multiplet
m/z	Mass per Charge
MHz	Mega Hertz
min	minute
mL	Millilitre
MS	Mass Spectrometry
MVDA	multivariate data analysis
^{o}C	Degree in Celsius
OPLS-DA	Orthogonal Partial Least Squares–Discriminant Analysis
PC	Principal Component
PCA	Principal Component Analysis
PLS	Partial Least Squares
PLS-DA	Partial Least Squares–Discriminant Analysis
ppm	Part Per Million
QTOF	Quadrupole–Time of Flight mass spectrometer

ROS	Reactive Oxygen Species
s	Singlet
SIMCA	Soft Independent Modelling of Class Analogy
TPC	Total Phenolic Contents
UV	Ultraviolet
UV/VIS	Ultraviolet/visible
VIP	variable importance in the projection
δ	Chemical Shift in ppm
µg	Microgram
µL	Microliter
^{13}C	Carbon-13

CHAPTER 1

INTRODUCTION

1.1 Background

Diabetes is a metabolic disorder usually characterized by hyperglycemia due to defects in insulin action, insulin secretion or both. Most of diabetes cases fall into two main etiopathogenetic categories. Type 1 diabetes mellitus (T1DM) results due to absolute deficiency of insulin secretion. The other category is type 2 diabetes mellitus (T2DM) caused by combination of resistance to insulin action and an insufficient compensatory insulin secretory response. Type 2 diabetes mellitus accounts for 90– 95% of all diabetes cases (Inzucchi et al. 2010). Currently, around 387 million people are living with this disease all over the world, and the number is expected to increase up to 592 million by the year 2035 (Guariguata et al. 2014).

T2DM is a complex type of diabetes and may results in multiple complications including micro-vascular complications, retinopathy, nephropathy and neuropathy etc., (Fowler 2011).

Imbalance between antioxidant defences and reactive oxygen species (ROS) production causes oxidative stress, which can increase from rising generation and /or decreased elimination of ROS by antioxidant. Consequently, excess production of ROS and impairment of the antioxidant defence system leads to diabetes mellitus. In this regard, any substance that delays or inhibits or removes the oxidative stress is defined as antioxidant (Halliwell 2011). Some prospective studies support the assumption that the progress of type 2 diabetes may be reduced by the consumption of antioxidant-rich diets (Porter 2012).

The existing pharmacological treatment options based on sulfonylureas, thiazolidinedione, and metformin, do not improve adequately the underlying consequences of insulin resistance such as hyperglycemia, pancreatic β-cell damage and diabetic dyslipidaemia (Goldberg, Holman, and Drucker 2008). Although currently a number of effective Western medications are available for the treatment of T2DM, management of T2DM at lower cost with fewer side effects still remain a big challenge. These Western medicines although effective, but can have severe side effects including weight gain, increased risk of cardiovascular events and bone loss (Fowler 2011). These side effects could become more severe due to the continuous use of these synthetic drugs. Comparatively, herbal medications can be considered as good alternative with fewer side effects and low cost. Herbal medications can treat diabetes by number of curatives such as stimulation of insulin secretion, enhancement of insulin sensitivity, and/or reduction of carbohydrate absorption (Li et al. 2004, Prabhakar and Doble 2011). Unlike Western medicine, herbal medicines may contain numerous active ingredients targeting multiple mechanisms and therefore herbal medicine can be considered as potential candidate for the treatment

of diabetes and its associated complications (Ceylan-Isik et al. 2008). Moreover, medicinal plants/ herbal medicine can not only be used as food supplementation but also in combination with Western medicine for better therapeutic outcomes.

Recently, search for antidiabetic medicines has now been extended to medicinal plants for the not only better management of diabetes mellitus with least side effects but also upgrade and prevent β-cell failure (Ohkita, Kiso, and Matsumura 2011, Zhao et al. 2011).

Recent studies established positive link between the plants and the decrease of chronic diseases, like diabetes mellitus (Bansal et al. 2012, Lee et al. 2014). Around 800 medicinal plants have been evaluated for their anti-diabetic potential for treatment or/and prevention of T2DM. (Prabhakar and Doble 2011). The natural product research is growing positively over the years and with improved "omics" technologies provides a platform to link traditional medicine and molecular pharmacology (Solanky et al. 2003, Wang, Lamers, et al. 2005, Yuliana et al. 2011). Out of all available "omics" technology, metabolomics is the latest which is recognized to be highly beneficial for the qualitative and quantitative characterization of all metabolites present in a cell, tissue, or/and organism under specific conditions (Colquhoun 2007). This emerging research field combines analytical chemistry, biochemistry and chemometrics and is highly emphatic for the analysis of thousands of small metabolites in any biological system. Mass spectrometry (MS) hyphenated with other analytical tools such as gas chromatography (GC), liquid chromatography (LC), nuclear magnetic resonance (NMR) spectroscopy and /or capillary electrophoresis (CE) are being used (Roessner and Beckles 2009). Comparatively for the monitoring of many endogenous "low-molecular-weight" metabolites LC/MS, NMR, and GC/M are the leading analytical plate forms (Bjerrum et al. 2009).

Use of animal model is highly imperative for the better understanding of metabolic disorders. Simulation of diabetic conditions based on animal model has been carried out by numerous researchers worldwide to explore the underlying molecular aspects and complications of this disease (Beckonert et al. 2007a, Tian et al. 2013).

Recently, metabolomics has been successfully applied by the researchers for the diagnosis and evaluation of the therapeutic effects linked with diabetes mellitus (DM) and its complications (Wu et al. 2014, Liu, Wang, et al. 2015). Numerous studies have been conducted previously with NMR-based metabolomics for the effective characterization of metabolites in serum, urine, or kidney tissue samples using diabetic rat models (Zhao et al. 2010, Tian et al. 2013, Emwas et al. 2015). So, metabolomics exhibit potential to identify overall alteration in metabolite levels during the treatments of diabetic cases.

Malaysia with its extensive flora presents an untapped capacity for the natural product research. *Melicope lunu-ankenda* (ML) is one of the *Melicope* species belonging to family Rutaceae and found all around the world especially in tropical

Asia and Australia. In Malaysia twenty-four *Melicope* species have been identified (Kassim et al. 2013). Its leaves are popular as salad and condiment for food flavoring. The leaves and flower are also traditionally being consumed to manage hypertension, menstrual disorder and fever etc. (Ramli et al. 2004, Tan, Yin, and Chan 2012). Presence of secondary metabolites including; alkaloids, flavonoids, acetophenones and coumarins in several *Melicope* species further ascertain its emphatic health benefits (Fauvel et al. 1981, Parsons et al. 1994). However, there are no reported on antidiabetic effects of this plant in high fat diet (HFD) rats and induced into diabetic condition with a low-dose of streptozotocin (STZ).

1.2 Problem Statement

Present study is therefore aimed at evaluating the *Melicope lunu-ankenda* extract for its functionalities i.e., antioxidant and antidiabetic potential both *in vitro* and *in vivo*. It is also identify the main bioactive compounds (in plant) and detects the biomarkers (animal bio-fluids) relating to antidiabetic effect of standardized ML extract on obese diabetic rats and subsequently to establish its efficacy as potent natural antidiabetic agent that may be used as functional foods or as natural alternative or in combinations to the conventional drugs for the treatment of diabetes mellitus.

1.3 Hypothesis

This study hypothesizes that animal model of HFD induced diabetes may be linked with many perturbations in serum biochemistry and metabolic pathways. The leaf extract of ML may show therapeutic efficacy *in vivo* study. It is expected that a ^{1}H NMR metabolomics method combined with suitable multivariate data analysis may be a good method to study these perturbations and the therapeutic effect of ML leaf extract.

1.4 Objectives of the study

1. To evaluate antidiabetic and antioxidant property of ML leaf extract.
2. To profile the bioactive compounds in ML leaf extract.
3. To evaluate the anti-diabetic activity of ML extract in obese diabetic Sprague-Dawley.
4. To determine the metabolic perturbations of obese diabetic Sprague-Dawley and the therapeutic effects of ML leaf extract.

REFERENCES

Abas, F., A. Khatib, V. Perumal, V. Suppaiah, A. Ismail, M. Hamid, K. Shaari, and N. H. Lajis. 2016. "Metabolic alteration in obese diabetes rats upon treatment with Centella asiatica extract." *Journal of ethnopharmacology*.180:60-69.

Abas, Faridah, Nordin H. Lajis, D. A. Israf, S. Khozirah, and Y. Umi Kalsom. 2006. "Antioxidant and nitric oxide inhibition activities of selected Malay traditional vegetables." *Food Chemistry* no. 95 (4):566-573.

Abourashed, Ehab A. 2013. "Bioavailability of Plant-Derived Antioxidants." *Antioxidants* no. 2 (4):309-325.

Ahamad, Javed, Kamran J. Naquvi, Showkat R. Mir, Mohd Ali, and Mohd Shuaib. 2011. "Review on Role of Natural Alpha-Glucosidase Inhibitors For Management of Diabetes Mellitus." *International Journal of Biomedical Research, 2*(6):374-380.

Albaayit, Shaymaa Fadhel Abbas, Yusuf Abba, Rasedee Abdullah, and Noorlidah Abdullah. 2014. "Evaluation of antioxidant activity and acute toxicity of Clausena excavata leaves extract." *Evidence-Based Complementary and Alternative Medicine* no. 2014:1-10.

Allwood, J. William, and Royston Goodacre. 2010. "An introduction to liquid chromatography–mass spectrometry instrumentation applied in plant metabolomic analyses." *Phytochemical Analysis* no. 21 (1):33-47.

Arise, Rotimi O., Aderounmu I. Ganiyu, and Oluwafemi O. Oguntibeju. 2014. "Lipid profile, antidiabetic and antioxidant activity of Acacia ataxacantha bark extract in streptozotocin-induced diabetic rats." *Antioxidant-antidiabetic Agents and Human Health. InTech Croatia*, 3-24.

Arts, Ilja C. W., and Peter C. H. Hollman. 2005. "Polyphenols and disease risk in epidemiologic studies." *The American journal of clinical nutrition* no. 81 (1):317S-325S.

Ashish, Baldi, Goyal Swapnil, and Ashish Baldi. 2011. "Hypoglycemic effect of polyherbal formulation in alloxan induced diabetic rats." *Pharmacologyonline* no. 3:764-773.

Astarita, Giuseppe, and James Langridge. 2013. "An emerging role for metabolomics in nutrition science." *Journal of nutrigenetics and nutrigenomics* no. 6 (4-5):181-200.

Atherton, Helen J., Nigel J. Bailey, Wen Zhang, John Taylor, Hilary Major, John Shockcor, Kieran Clarke, and Julian L. Griffin. 2006. "A combined 1H-NMR spectroscopy-and mass spectrometry-based metabolomic study of the PPAR-α null mutant mouse defines profound systemic changes in metabolism linked to the metabolic syndrome." *Physiological genomics* no. 27 (2):178-186.

Avery, Mitchell A., Cassia S. Mizuno, Amar G. Chittiboyina, Theodore W. Kurtz, and Harrihar A. Pershadsingh. 2008. "Type 2 diabetes and oral antihyperglycemic drugs." *Current medicinal chemistry* no. 15 (1):61-74.

Aydin, Ebru. 2015. "Effects of Natural Products on Sugar Metabolism and Digestive Enzymes." PhD dissertation., University of Leeds.

Bain, James R., Robert D. Stevens, Brett R. Wenner, Olga Ilkayeva, Deborah M. Muoio, and Christopher B. Newgard. 2009. "Metabolomics applied to diabetes research moving from information to knowledge." *Diabetes* no. 58 (11):2429-2443.

Bair, Eric, Trevor Hastie, Debashis Paul, and Robert Tibshirani. 2012. "Prediction by supervised principal components." *Journal of the American Statistical Association*.

Balamurugan, Rangachari, Veeramuthu Duraipandiyan, and Savarimuthu Ignacimuthu. 2011. "Antidiabetic activity of γ-sitosterol isolated from Lippia nodiflora L. in streptozotocin induced diabetic rats." *European journal of pharmacology* no. 667 (1):410-418.

Bansal, Punit, Piya Paul, Jayesh Mudgal, Pawan G. Nayak, Steve Thomas Pannakal, K. I. Priyadarsini, and M. K. Unnikrishnan. 2012. "Antidiabetic, antihyperlipidemic and antioxidant effects of the flavonoid rich fraction of Pilea microphylla (L.) in high fat diet/streptozotocin-induced diabetes in mice." *Experimental and Toxicologic Pathology* no. 64 (6):651-658.

Barnes, Stephen, Jeevan Prasain, and Helen Kim. 2013. "In Nutrition, Can We "See" What Is Good for Us?" *Advances in Nutrition: An International Review Journal* no. 4 (3):327S-334S.

Basavaraj, Doddametikurke Ramegowda, Chandra Shekhar Biyani, Anthony J. Browning, and Jon J. Cartledge. 2007. "The role of urinary kidney stone inhibitors and promoters in the pathogenesis of calcium containing renal stones." *EAU-EBU update series* no. 5 (3):126-136.

Batch, Bryan C., Kristen Hyland, and Laura P. Svetkey. 2014. "Branch chain amino acids: biomarkers of health and disease." *Current Opinion in Clinical Nutrition & Metabolic Care* no. 17 (1):86-89.

Bays, Harold, Lawrence Mandarino, and Ralph A. Defronzo. 2004. "Role of the adipocyte, free fatty acids, and ectopic fat in pathogenesis of type 2 diabetes mellitus: peroxisomal proliferator-activated receptor agonists provide a rational therapeutic approach." *The Journal of Clinical Endocrinology & Metabolism* no. 89 (2):463-478.

Beckonert, Hector C. Keun, Timothy M. D. Ebbels, Jacob Bundy, Elaine Holmes, John C. Lindon, and Jeremy K. Nicholson. 2007a. "Metabolic profiling, metabolomic and metabonomic procedures for NMR spectroscopy of urine, plasma, serum and tissue extracts." *Nature protocols* no. 2 (11):2692-2703.

Beckonert, Olaf, Hector C. Keun, Timothy M. D. Ebbels, Jacob Bundy, Elaine Holmes, John C. Lindon, and Jeremy K. Nicholson. 2007b. "Metabolic profiling, metabolomic and metabonomic procedures for NMR spectroscopy

of urine, plasma, serum and tissue extracts." *Nature protocols* no. 2 (11):2692-2703.

Beecher, Gary R. 2003. "Overview of dietary flavonoids: nomenclature, occurrence and intake." *The Journal of nutrition* no. 133 (10):3248S-3254S.

Bell, J. D., P. J. Sadler, V. C. Morris, and O. A. Levander. 1991. "Effect of aging and diet on proton NMR spectra of rat urine." *Magnetic resonance in medicine* no. 17 (2):414-422.

Bertozzi, Carolyn R., and Laura L. Kiessling. 2001. "Chemical glycobiology." *Science* no. 291 (5512):2357-2364.

Bictash, Magda, Timothy Ebbels, Queenie Chan, Ruey Leng Loo, Ivan Yap, Ian J. Brown, Maria De Iorio, Martha Daviglus, Elaine Holmes, and Jeremiah Stamler. 2010. "Metabolic phenotyping in epidemiology and metabolome-wide association studies." *Journal of clinical epidemiology* no. 63 (9):970.

Bischoff, Hilmar. 1995. "The mechanism of alpha-glucosidase inhibition in the management of diabetes." *Clinical and investigative medicine. Médecine clinique et experimentale* no. 18 (4):303-311.

Bjerrum, Jacob T., Ole H. Nielsen, Fuhua Hao, Huiru Tang, Jeremy K. Nicholson, Yulan Wang, and Jørgen Olsen. 2009. "Metabonomics in ulcerative colitis: diagnostics, biomarker identification, and insight into the pathophysiology." *Journal of proteome research* no. 9 (2):954-962.

Boada, C. A. Carrera, and J. M. Martinez-Moreno. 2013. "Pathophysiology of diabetes mellitus type 2: beyond the duo "insulin resistance-secretion deficit"." *Nutr Hosp* no. 28 (Supl 2):78-87.

Boden, Guenther, Xinhua Chen, and T. Peter Stein. 2001. "Gluconeogenesis in moderately and severely hyperglycemic patients with type 2 diabetes mellitus." *American Journal of Physiology-Endocrinology And Metabolism* no. 280 (1):E23-E30.

Boden, Guenther, Peter Cheung, T. Peter Stein, Karen Kresge, and Maria Mozzoli. 2002. "FFA cause hepatic insulin resistance by inhibiting insulin suppression of glycogenolysis." *American Journal of Physiology-Endocrinology and Metabolism* no. 283 (1):E12-E19.

Brand-Williams, W., M. E. Cuvelier, and Clwt Berset. 1995. "Use of a free radical method to evaluate antioxidant activity." *LWT-Food Science and Technology* no. 28 (1):25-30.

Brand, Martin D. 2010. "The sites and topology of mitochondrial superoxide production." *Experimental gerontology* no. 45 (7):466-472.

Brennan, Lorraine, Aine Shine, Chandralal Hewage, J. Paul G. Malthouse, Kevin M. Brindle, Neville McClenaghan, Peter R. Flatt, and Philip Newsholme. 2002. "A nuclear magnetic resonance-based demonstration of substantial oxidative L-alanine metabolism and L-alanine-enhanced glucose metabolism in a clonal pancreatic β-cell line metabolism of L-alanine is important to the regulation of insulin secretion." *Diabetes* no. 51(6):1714-1721.

Brien, Richard M., and Daryl K. Granner. 1996. "Regulation of gene expression by insulin." *Physiological Reviews* no. 76 (4):1109-1161.

Brown, Marie, David C. Wedge, Royston Goodacre, Douglas B. Kell, Philip N. Baker, Louise C. Kenny, Mamas A. Mamas, Ludwig Neyses, and Warwick B. Dunn. 2011. "Automated workflows for accurate mass-based putative metabolite identification in LC/MS-derived metabolomic datasets." *Bioinformatics* no. 27 (8):1108-1112.

Browning, Kirsteen N., Samuel R. Fortna, and Andras Hajnal. 2013. "Roux-en-Y gastric bypass reverses the effects of diet-induced obesity to inhibit the responsiveness of central vagal motoneurones." *The Journal of physiology* no. 591 (9):2357-2372.

Brownlee, Michael. 2005. "The pathobiology of diabetic complications a unifying mechanism." *Diabetes* no. 54 (6):1615-1625.

Brusotti, G., I. Cesari, A. Dentamaro, G. Caccialanza, and G. Massolini. 2014. "Isolation and characterization of bioactive compounds from plant resources: The role of analysis in the ethnopharmacological approach." *Journal of pharmaceutical and biomedical analysis* no. 87:218-228.

Buettner, R., K. G. Parhofer, M. Woenckhaus, C. E. Wrede, L. A. Kunz-Schughart, J. Schölmerich, and L. C. Bollheimer. 2006. "Defining high-fat-diet rat models: metabolic and molecular effects of different fat types." *Journal of molecular endocrinology* no. 36 (3):485-501.

Büscher, Jörg Martin, Dominika Czernik, Jennifer Christina Ewald, Uwe Sauer, and Nicola Zamboni. 2009. "Cross-platform comparison of methods for quantitative metabolomics of primary metabolism." *Analytical chemistry* no. 81 (6):2135-2143.

Butler, Alexandra E., Juliette Janson, Susan Bonner-Weir, Robert Ritzel, Robert A. Rizza, and Peter C. Butler. 2003. "β-cell deficit and increased β-cell apoptosis in humans with type 2 diabetes." *Diabetes* no. 52 (1):102-110.

Butterfield, D. Allan, Tanuja Koppal, Beverly Howard, R. A. M. Subramaniam, Nathan Hall, Kenneth Hensley, Servet Yatin, Kerry Allen, Michael Aksenov, and Marina Aksenova. 1998. "Structural and Functional Changes in Proteins Induced by Free Radical-mediated Oxidative Stress and Protective Action of the Antioxidants N-tert-Butyl-α-phenylnitrone and Vitamin Ea." *Annals of the New York Academy of Sciences* no. 854 (1):448-462.

Bylesjö, Max, Mattias Rantalainen, Olivier Cloarec, Jeremy K. Nicholson, Elaine Holmes, and Johan Trygg. 2006. "OPLS discriminant analysis: combining the strengths of PLS-DA and SIMCA classification." *Journal of Chemometrics* no. 20 (8-10):341-351.

Cacace, J. E., and G. Mazza. 2003. "Optimization of extraction of anthocyanins from black currants with aqueous ethanol." *Journal of Food Science* no. 68 (1):240-248.

Cacciatore, Stefano, and Massimo Loda. 2015. "Innovation in metabolomics to improve personalized healthcare." *Annals of the New York Academy of Sciences* no. 1346 (1):57-62.

Cai, Erica P., and Jen-Kun Lin. 2009. "Epigallocatechin gallate (EGCG) and rutin suppress the glucotoxicity through activating IRS2 and AMPK signaling in rat pancreatic β cells." *Journal of agricultural and food chemistry* no. 57 (20):9817-9827.

Cattell, Raymond B. 1966. "The scree test for the number of factors." *Multivariate behavioral research* no. 1 (2):245-276.

Cefalu, W. T., J. M. Stephens, and D. M. Ribnicky. 2011. "Diabetes and Herbal (Botanical) Medicine."

Ceriello, Antonio, and Enrico Motz. 2004. "Is oxidative stress the pathogenic mechanism underlying insulin resistance, diabetes, and cardiovascular disease? The common soil hypothesis revisited." *Arteriosclerosis, thrombosis, and vascular biology* no. 24 (5):816-823.

Cevallos-Cevallos, Juan Manuel, and José Ignacio Reyes-De-Corcuera. 2012. "Metabolomics in food science." *Adv. Food Nutr. Res* no. 67:1-24.

Ceylan-Isik, Asli F., Rochelle M. Fliethman, Loren E. Wold, and Jun Ren. 2008. "Herbal and traditional Chinese medicine for the treatment of cardiovascular complications in diabetes mellitus." *Current Diabetes Reviews* no. 4 (4):320-328.

Chaalal, Makhlouf, Noureddine Touati, and Hayette Louaileche. 2012. "Extraction of phenolic compounds and *in vitro* antioxidant capacity of prickly pear seeds." *Acta Botanica Gallica* no. 159 (4):467-475.

Chen, Jih-Jung, Chang-Yih Duh, Hung-Yi Huang, and Ih-Sheng Chen. 2003. "Furoquinoline alkaloids and cytotoxic constituents from the leaves of *Melicope semecarpifolia*." *Planta medica* no. 69 (6):542-546.

Chen, Xiaolong, Yuguo Zheng, and Yinchu Shen. 2006. "Voglibose (Basen®, AO-128), one of the most important α-glucosidase inhibitors." *Current medicinal chemistry* no. 13 (1):109-116.

Chew, K. K., M. Z. Khoo, S. Y. Ng, Y. Y. Thoo, W. M. Wan Aida, and C. W. Ho. 2011. "Effect of ethanol concentration, extraction time and extraction temperature on the recovery of phenolic compounds and antioxidant capacity of Orthosiphon stamineus extracts." *International Food Research Journal* no. 18 (4).

Cho, Hyun-Woo, Seoung Bum Kim, Myong K. Jeong, Youngja Park, Nana Miller, Thomas Ziegler, and Dean Jones. 2008. "Discovery of metabolite features for the modelling and analysis of high-resolution NMR spectra." *International journal of data mining and bioinformatics* no. 2 (2): 176-192.

Cloarec, Olivier, Marc-Emmanuel Dumas, Andrew Craig, Richard H. Barton, Johan Trygg, Jane Hudson, Christine Blancher, Dominique Gauguier, John C. Lindon, and Elaine Holmes. 2005. "Statistical total correlation spectroscopy:

an exploratory approach for latent biomarker identification from metabolic 1H NMR data sets." *Analytical chemistry* no. 77 (5):1282-1289.

Colquhoun, Ian J. 2007. "Use of NMR for metabolic profiling in plant systems." *Journal of Pesticide Science* no. 32 (3):200-212.

Connor, Susan C., Michael K. Hansen, Adam Corner, Randall F. Smith, and Terence E. Ryan. 2010. "Integration of metabolomics and transcriptomics data to aid biomarker discovery in type 2 diabetes." *Molecular BioSystems* no. 6 (5):909-921.

Danda, Ratna S., Nusrath M. Habiba, Hernan Rincon-Choles, Basant K. Bhandari, Jeffrey L. Barnes, Hanna E. Abboud, and Pablo E. Pergola. 2005. "Kidney involvement in a nongenetic rat model of type 2 diabetes." *Kidney international* no. 68 (6):2562-2571.

Dangles, Olivier, Claire Dufour, Claudine Manach, Christine Morand, and Christian Remesy. 2001. "Binding of flavonoids to plasma proteins." *Methods in enzymology* no. 335:319-333.

Darmawan, Akhmad, Soleh Kosela, Leonardus Kardono, and Yana M. Syah. 2012. "Scopoletin, a coumarin derivative compound isolated from Macaranga gigantifolia Merr."

Das, Undurti N. 2006. "Essential fatty acids: biochemistry, physiology and pathology." *Biotechnology journal* no. 1 (4):420-439.

Day, Andrea J., Yongping Bao, Michael R. A. Morgan, and Gary Williamson. 2000. "Conjugation position of quercetin glucuronides and effect on biological activity." *Free Radical Biology and Medicine* no. 29 (12):1234-1243.

De Hoffmann, E., and V. Stroobant. "Mass spectrometry: principles and applications. 2007." *Iohn Wiley* no. 8.

de M Bandeira, Suziy, Lucas Jos é S. da Fonseca, Glaucevane da S Guedes, Lu ź a A. Rabelo, Mar Ília O. F. Goulart, and Sandra Mary L. Vasconcelos. 2013. "Oxidative stress as an underlying contributor in the development of chronic complications in diabetes mellitus." *International journal of molecular sciences* no. 14 (2):3265-3284.

Deguchi, Tsuneo, Mizue Takemoto, Nao Uehara, W. Edward Lindup, Ayaka Suenaga, and Masaki Otagiri. 2005. "Renal clearance of endogenous hippurate correlates with expression levels of renal organic anion transporters in uremic rats." *Journal of Pharmacology and Experimental Therapeutics* no. 314 (2):932-938.

Deng, Ming-Jie, Xiao-Dong Lin, Qiu-Ting Lin, De-Fu Wen, Mei-Ling Zhang, Xian-Qin Wang, Hong-Chang Gao, and Jia-Ping Xu. 2015. "A 1 H-NMR based study on hemolymph metabolomics in eri silkworm after oral administration of 1-deoxynojirimycin." *PloS one* no. 10 (7):e0131696.

Deng, Wen-Jun, Song Nie, Jie Dai, Jia-Rui Wu, and Rong Zeng. 2010. "Proteome, phosphoproteome, and hydroxyproteome of liver mitochondria in diabetic rats at early pathogenic stages." *Molecular & Cellular Proteomics* no. 9 (1):100-116.

Derosa, Giuseppe, Pamela Maffioli, Ilaria Ferrari, Elena Fogari, Angela D'Angelo, Ilaria Palumbo, Sabrina Randazzo, Lucio Bianchi, and Arrigo F. G. Cicero. 2011. "Acarbose actions on insulin resistance and inflammatory parameters during an oral fat load." *European journal of pharmacology* no. 651 (1):240-250.

Dettmer, K., P. A. Aronov, and B. D. Hammock. 2007. "Mass spectrometry-based metabolomics." *Mass Spectrom Rev* no. 26 (1):51-78. doi: 10.1002/mas.20108.

Diao, Chengfeng, Liangcai Zhao, Mimi Guan, Yongquan Zheng, Minjiang Chen, Yunjun Yang, Li Lin, Weijian Chen, and Hongchang Gao. 2014"Systemic and characteristic metabolites in the serum of streptozotocin-induced diabetic rats at different stages as revealed by a 1 H-NMR based metabonomic approach." *Molecular bioSystems* no.10 (3): 686-693.

Dias, Daniel A., Sylvia Urban, and Ute Roessner. 2012. "A historical overview of natural products in drug discovery." *Metabolites* no. 2 (2): 303-336.

Di Gialleonardo, Valentina, Erik F. J. de Vries, Marco Di Girolamo, Ana M. Quintero, Rudi A. J. O. Dierckx, and Alberto Signore. 2012. "Imaging of β-cell mass and insulitis in insulin-dependent (type 1) diabetes mellitus." *Endocrine reviews* no. 33 (6):892-919.

Donga, J. J., V. S. Surani, G. U. Sailor, S. P. Chauhan, and A. K. Seth. 2011. "A systematic review on natural medicine used for therapy of diabetes mellitus of some Indian medicinal plants." *Pharm Sci Monit* no. 2 (1):36-72.

Dorababu, M., T. Prabha, S. Priyambada, V. K. Agrawal, N. C. Aryya, and R. K. Goel. 2004. "Effect of Bacopa monniera and Azadirachta indica on gastric ulceration and healing in experimental NIDDM rats." *Indian journal of experimental biology* no. 42 (4):389-397.

Dixon, G., J. Nolan, Neville McClenaghan, P. R. Flatt, and P. Newsholme. 2003 "A comparative study of amino acid consumption by rat islet cells and the clonal beta-cell line BRIN-BD11-the functional significance of L-alanine." *Journal of Endocrinology* no. 179 (3): 447-454.

Dragan, S., F. Andrica, Maria-Corina Serban, and R. Timar. 2015. "Polyphenols-rich natural products for treatment of diabetes." *Current medicinal chemistry* no. 22 (1):14-22.

Du, Fuyong, Anthony Virtue, Hong Wang, and Xiao-Feng Yang. 2013. "Metabolomic analyses for atherosclerosis, diabetes, and obesity." *Biomarker Res* no. 1:17.

Dumas, Marc-Emmanuel, Richard H. Barton, Ayo Toye, Olivier Cloarec, Christine Blancher, Alice Rothwell, Jane Fearnside, Roger Tatoud, Véronique Blanc, and John C. Lindon. 2006. "Metabolic profiling reveals a contribution of gut microbiota to fatty liver phenotype in insulin-resistant mice." *Proceedings of the national academy of sciences* no. 103 (33):12511-12516.

Dunn, Warwick B., Alexander Erban, Ralf J. M. Weber, Darren J. Creek, Marie Brown, Rainer Breitling, Thomas Hankemeier, Royston Goodacre, Steffen

Neumann, and Joachim Kopka. 2013. "Mass appeal: metabolite identification in mass spectrometry-focused untargeted metabolomics." *Metabolomics* no. 9 (1):44-66.

Dunn, Warwick B., Royston Goodacre, Ludwig Neyses, and Mamas Mamas. 2011. "Integration of metabolomics in heart disease and diabetes research: current achievements and future outlook." *Bioanalysis* no. 3 (19):2205-2222.

Durmuşkahya, C., and M. Öztürk. 2013. "Ethnobotanical survey of medicinal plants used for the treatment of diabetes in Manisa, Turkey." *Sains Malaysiana* no. 42 (10):1431-1438.

Eddouks, M., M. Maghrani, A. Lemhadri, M. L. Ouahidi, and H. Jouad. 2002. "Ethnopharmacological survey of medicinal plants used for the treatment of diabetes mellitus, hypertension and cardiac diseases in the south-east region of Morocco (Tafilalet)." *Journal of ethnopharmacology* no. 82 (2):97-103.

El-Assaad, Wissal, Jean Buteau, Marie-Line Peyot, Christopher Nolan, Raphael Roduit, Serge Hardy, Erik Joly, Ghassan Dbaibo, Lawrence Rosenberg, and Marc Prentki. 2003. "Saturated fatty acids synergize with elevated glucose to cause pancreatic β-cell death." *Endocrinology* no. 144 (9):4154-4163.

Emwas, Abdul-Hamid, Claudio Luchinat, Paola Turano, Leonardo Tenori, Raja Roy, Reza M. Salek, Danielle Ryan, Jasmeen S. Merzaban, Rima Kaddurah-Daouk, and Ana Carolina Zeri. 2015. "Standardizing the experimental conditions for using urine in NMR-based metabolomic studies with a particular focus on diagnostic studies: a review." *Metabolomics* no. 11 (4):872-894.

Epstein, Franklin H., Peter R. Shepherd, and Barbara B. Kahn. 1999. "Glucose transporters and insulin action—implications for insulin resistance and diabetes mellitus." *New England Journal of Medicine* no. 341 (4):248-257.

Eriksson, Lennart, Nouna Kettaneh-Wold, Johan Trygg, Conny Wikström, and Svante Wold. 2006. "Multi-and megavariate data analysis: Part I: basic principles and applications."

Esmaeili, Mohammad Ali, and Razieh Yazdanparast. 2004. "Hypoglycaemic effect of Teucrium polium: studies with rat pancreatic islets." *Journal of Ethnopharmacology* no. 95 (1):27-30.

Esterbauer, Hermann, Rudolf J. rg Schaur, and Helmward Zollner. 1990. "Chemistry and biochemistry of 4-hydroxynonenal, malonaldehyde and related aldehydes." *Free radical biology & medicine* no. 11 (1):81-128.

Fauvel, M. Th, J. Gleye, C. Moulis, F. Blasco, and E. Stanislas. 1981. "Alkaloids and flavonoids of *Melicope indica*." *Phytochemistry* no. 20 (8):2059-2060. doi: http://dx.doi.org/10.1016/0031-9422(81)84078-2.

Feng, Jie, Xiu-Wei Yang, and Ru-Feng Wang. 2011. "Bio-assay guided isolation and identification of α-glucosidase inhibitors from the leaves of Aquilaria sinensis." *Phytochemistry* no. 72 (2):242-247.

Ferrannini, Ele, Andrea Natali, Stefania Camastra, Monica Nannipieri, Andrea Mari, Klaus-Peter Adam, Michael V. Milburn, Gabi Kastenmüller, Jerzy Adamski,

and Tiinamaija Tuomi. 2013. "Early metabolic markers of the development of dysglycemia and type 2 diabetes and their physiological significance." *Diabetes* no. 62 (5):1730-1737.

Festa, Andreas, Ken Williams, Anthony J. G. Hanley, James D. Otvos, David C. Goff, Lynne E. Wagenknecht, and Steven M. Haffner. 2005. "Nuclear magnetic resonance lipoprotein abnormalities in prediabetic subjects in the Insulin Resistance Atherosclerosis Study." *Circulation* no. 111 (25):3465-3472.

Floegel, Anna, Norbert Stefan, Zhonghao Yu, Kristin Mühlenbruch, Dagmar Drogan, Hans-Georg Joost, Andreas Fritsche, Hans-Ulrich Häring, Martin Hrabě de Angelis, and Annette Peters. 2013. "Identification of serum metabolites associated with risk of type 2 diabetes using a targeted metabolomic approach." *Diabetes* no. 62 (2):639-648.

Fowler, Michael J. 2011. "Microvascular and macrovascular complications of diabetes." *Clinical Diabetes* no. 29 (3):116-122.

Friedrich, Nele. 2012. "Metabolomics in diabetes research." *Journal of Endocrinology* no. 215 (1):29-42.

Fritsche, Louise, Cora Weigert, Hans-Ulrich Haring, and Rainer Lehmann. 2008. "How insulin receptor substrate proteins regulate the metabolic capacity of the liver-implications for health and disease." *Current medicinal chemistry* no. 15 (13):1316-1329.

Frost, Susan C., and M. Daniel Lane. 1985. "Evidence for the involvement of vicinal sulfhydryl groups in insulin-activated hexose transport by 3T3-L1 adipocytes." *Journal of Biological Chemistry* no. 260 (5):2646-2652.

Furukawa, Shigetada, Takuya Fujita, Michio Shimabukuro, Masanori Iwaki, Yukio Yamada, Yoshimitsu Nakajima, Osamu Nakayama, Makoto Makishima, Morihiro Matsuda, and Iichiro Shimomura. 2004. "Increased oxidative stress in obesity and its impact on metabolic syndrome." *The Journal of clinical investigation* no. 114 (12):1752-1761.

Gandhi, G. Rajiv, and P. Sasikumar. 2012. "Antidiabetic effect of Merremia emarginata Burm. F. in streptozotocin induced diabetic rats." *Asian Pacific journal of tropical biomedicine* no. 2 (4):281-286.

Gao, Min, and Chun-Zhao Liu. 2005. "Comparison of techniques for the extraction of flavonoids from cultured cells of Saussurea medusa Maxim." *World Journal of Microbiology and Biotechnology* no. 21 (8-9):1461-1463.

Gastaldelli, A., E. Ferrannini, Y. Miyazaki, M. Matsuda, and R. A. DeFronzo. 2004. "Beta-cell dysfunction and glucose intolerance: results from the San Antonio metabolism (SAM) study." *Diabetologia* no. 47 (1):31-39.

Gastaldelli, Amalia. 2011. "Role of beta-cell dysfunction, ectopic fat accumulation and insulin resistance in the pathogenesis of type 2 diabetes mellitus." *Diabetes research and clinical practice* no. 93:S60-S65.

George, Sony, S. Ajikumaran Nair, Anil J. Johnson, Ramaswamy Venkataraman, and Sabulal Baby. 2015. "O-prenylated flavonoid, an antidiabetes constituent in *Melicope lunu-ankenda*." *Journal of ethnopharmacology* no. 168:158-163.

Georgiev, M. I., K. Ali, K. Alipieva, R. Verpoorte, and Y. H. Choi. 2011. "Metabolic differentiations and classification of Verbascum species by NMR-based metabolomics." In *Phytochemistry*, 2045-51. United States: 2011 Elsevier Ltd.

Ghasemzadeh, Ali, and Neda Ghasemzadeh. 2011. "Flavonoids and phenolic acids: Role and biochemical activity in plants and human." *Journal of medicinal plants research* no. 5 (31):6697-6703.

Gholap, S., and A. Kar. 2004. "Hypoglycaemic effects of some plant extracts are possibly mediated through inhibition in corticosteroid concentration." *Die Pharmazie-An International Journal of Pharmaceutical Sciences* no. 59 (11):876-878.

Gidh-Jain, M., J. Takeda, L. Z. Xu, A. J. Lange, N. Vionnet, M. Stoffel, P. Froguel, G. Velho, F. Sun, and David Cohen. 1993. "Glucokinase mutations associated with non-insulin-dependent (type 2) diabetes mellitus have decreased enzymatic activity: implications for structure/function relationships." *Proceedings of the National Academy of Sciences* no. 90 (5):1932-1936.

Glauser, Gaetan, Davy Guillarme, Elia Grata, Julien Boccard, Aly Thiocone, Pierre-Alain Carrupt, Jean-Luc Veuthey, Serge Rudaz, and Jean-Luc Wolfender. 2008. "Optimized liquid chromatography–mass spectrometry approach for the isolation of minor stress biomarkers in plant extracts and their identification by capillary nuclear magnetic resonance." *Journal of Chromatography A* no. 1180 (1):90-98.

Göke, B., C. Herrmann, R. Göke, H. C. Fehmann, P. Berghöfer, G. Richter, and R. Arnold. 1994. "Intestinal effects of α-glucosidase inhibitors: absorption of nutrients and enterohormonal changes." *European journal of clinical investigation* no. 24 (S3):25-30.

Goldberg, Ronald B., Rury Holman, and Daniel J. Drucker. 2008. "Management of type 2 diabetes." *The New England journal of medicine* no. 358 (3):293-297.

Goodacre, Royston, David Broadhurst, Age K. Smilde, Bruce S. Kristal, J. David Baker, Richard Beger, Conrad Bessant, Susan Connor, Giorgio Capuani, and Andrew Craig. 2007. "Proposed minimum reporting standards for data analysis in metabolomics." *Metabolomics* no. 3 (3):231-241.

Gougeon, Réjeanne, José A. Morais, Stéphanie Chevalier, Sandra Pereira, Marie Lamarche, and Errol B. Marliss. 2008. "Determinants of whole-body protein metabolism in subjects with and without type 2 diabetes." *Diabetes care* no. 31 (1):128-133.

Govers, Roland. 2014. "Cellular regulation of glucose uptake by glucose transporter GLUT4." *Adv Clin Chem* no. 66:173-240.

Gowda, G. A. Nagana, Shucha Zhang, Haiwei Gu, Vincent Asiago, Narasimhamurthy Shanaiah, and Daniel Raftery. 2008. "Metabolomics-based methods for early disease diagnostics." *Expert review of molecular diagnostics* no. 8 (5):617-633.

Graf, Brigitte A., Paul E. Milbury, and Jeffrey B. Blumberg. 2005. "Flavonols, flavones, flavanones, and human health: epidemiological evidence." *Journal of medicinal food* no. 8 (3):281-290.

Grover, JK, S Yadav, and V Vats. 2002. "Medicinal plants of India with anti-diabetic potential." *Journal of ethnopharmacology* no. 81 (1):81-100.

Guan, Mimi, Liyun Xie, Chengfeng Diao, Na Wang, Wenyi Hu, Yongquan Zheng, Litai Jin, Zhihan Yan, and Hongchang Gao. 2013. "Systemic perturbations of key metabolites in diabetic rats during the evolution of diabetes studied by urine metabonomics." *PloS one* no. 8 (4):e60409.

Guariguata, L., D. R. Whiting, I. Hambleton, J. Beagley, U. Linnenkamp, and J. E. Shaw. 2014. "Global estimates of diabetes prevalence for 2013 and projections for 2035." *Diabetes research and clinical practice* no. 103 (2):137-149.

Gulati, Vandana, Pankaj Gulati, Ian H. Harding, and Enzo A. Palombo. 2015. "Exploring the anti-diabetic potential of Australian Aboriginal and Indian Ayurvedic plant extracts using cell-based assays." *BMC complementary and alternative medicine* no. 15 (1):1.

Guo, Changjiang, Jijun Yang, Jingyu Wei, Yunfeng Li, Jing Xu, and Yugang Jiang. 2003. "Antioxidant activities of peel, pulp and seed fractions of common fruits as determined by FRAP assay." *Nutrition Research* no. 23 (12):1719-1726.

Ha, Do Thi, Trinh Nam Trung, Nguyen Bich Thu, Tran Van On, Nguyen Hai Nam, Chu Van Men, Tran Thi Phuong, and KiHwan Bae. 2010. "Adlay seed extract (Coix lachryma-jobi L.) decreased adipocyte differentiation and increased glucose uptake in 3T3-L1 cells." *Journal of medicinal food* no. 13 (6):1331-1339.

Habeeb, M. Najma, Prakash R. Naik, and Fahmi S. Moqbel. 2012. "Inhibition of α-glucosidase and α-amylase by Morus alba Linn leaf extracts." *Journal of Pharmacy Research Vol* no. 5 (1):285-289.

Halim M, E. 2003. "Lowering of blood sugar by water extract of Azadirachta indica and Abroma augusta in diabetes rats." *Indian journal of experimental biology* no. 41 (6):636-640.

Halliwell, B., and J. M. C. Gutteridge. 2007. Free radicals in biology and medicine, 4th edn. Clarendon. Oxford.

Halliwell, Barry. 2011. "Free radicals and antioxidants–quo vadis?" *Trends in pharmacological sciences* no. 32 (3):125-130.

Han, X., A. B. Patters, D. P. Jones, I. Zelikovic, and R. W. Chesney. 2006. "The taurine transporter: mechanisms of regulation." *Acta Physiologica* no. 187 (1-2):61-73.

Hanhineva, K., R. Torronen, I. Bondia-Pons, J. Pekkinen, M. Kolehmainen, H. Mykkanen, and K. Poutanen. 2010. "Impact of dietary polyphenols on carbohydrate metabolism." *Int J Mol Sci* no. 11 (4):1365-402. doi: 10.3390/ijms11041365.

He, Zhengyou, Minbo Lan, Dongying Lu, Hongli Zhao, and Huihui Yuan. 2013. "Antioxidant Activity of 50 Traditional Chinese Medicinal Materials Varies with Total Phenolics." *Chinese Medicine* no. 4 (04):148.

Heidari, R., S. Zareae, and M. Heidarizadeh. 2005. "Extraction, purification, and inhibitory effect of alpha-amylase inhibitor from wheat (Triticum aestivum Var. Zarrin)." *Pakistan J Nutr* no. 4:101-105.

Heiner, L. 2002. "Acarbose an update of its therapeutic use in diabetes treatment." *Clin Drug Invest* no. 22:141-56.

Hollywood, Katherine, Daniel R. Brison, and Royston Goodacre. 2006. "Metabolomics: current technologies and future trends." *Proteomics* no. 6 (17):4716-4723.

Houstis, Nicholas, Evan D. Rosen, and Eric S. Lander. 2006. "Reactive oxygen species have a causal role in multiple forms of insulin resistance." *Nature* no. 440 (7086):944-948.

Huang, Dejian, Boxin Ou, and Ronald L. Prior. 2005. "The chemistry behind antioxidant capacity assays." *Journal of agricultural and food chemistry* no. 53 (6):1841-1856.

Huang, Xiaodong, and Fred E. Regnier. 2008. "Differential metabolomics using stable isotope labeling and two-dimensional gas chromatography with time-of-flight mass spectrometry." *Analytical chemistry* no. 80 (1):107-114.

Huang, Yu-Chuan, Cheng-Yu Lin, Su-Fen Huang, Han-Ching Lin, Wen-Liang Chang, and Tsu-Chung Chang. 2010. "Effect and mechanism of ginsenosides CK and Rg1 on stimulation of glucose uptake in 3T3-L1 adipocytes." *Journal of agricultural and food chemistry* no. 58 (10):6039-6047.

Hung, Hsin-Yi, Keduo Qian, Susan L. Morris-Natschke, Chau-Shin Hsu, and Kuo-Hsiung Lee. 2012. "Recent discovery of plant-derived anti-diabetic natural products." *Natural product reports* no. 29 (5):580-606.

Hunt, J. V., R. T. Dean, and S. P. Wolff. 1988. "Hydroxyl radical production and autoxidative glycosylation. Glucose autoxidation as the cause of protein damage in the experimental glycation model of diabetes mellitus and ageing." *Biochemical journal* no. 256 (1):205-212.

Hunter, Philip. 2009. "Reading the metabolic fine print." *EMBO reports* no. 10 (1):20-23.

Iacopini, P., M. Baldi, P. Storchi, and L. Sebastiani. 2008. "Catechin, epicatechin, quercetin, rutin and resveratrol in red grape: Content, *in vitro* antioxidant activity and interactions." *Journal of Food Composition and Analysis* no. 21 (8):589-598.

Inzucchi, Silvio, Richard Bergenstal, Vivian Fonseca, E'dward Gregg, Beth Mayer-Davis, Geralyn Spollett, and Richard Wender. 2010. "American Diabetes Association. Diagnosis and classification of diabetes mellitus." *Diabetes Care* no. 33.

Irondi, Emmanuel Anyachukwu, Ganiyu Oboh, and Afolabi Akintunde Akindahunsi. 2015. "Methanol extracts of Brachystegia eurycoma and Detarium microcarpum seeds flours inhibit some key enzymes linked to the pathology and complications of type 2 diabetes *in vitro*." *Food Science and Human Wellness* no. 4 (4):162-168.

Irondi, Emmanuel Anyachukwu, Ganiyu Oboh, Afolabi Akintunde Akindahunsi, Aline Augusti Boligon, and Margareth Linde Athayde. 2015. "Phenolics composition and antidiabetic property of Brachystegia eurycoma seed flour in high-fat diet, low-dose streptozotocin-induced type 2 diabetes in rats." *Asian Pacific Journal of Tropical Disease* no. 5:S159-S165.

Islam, M. Shahidul, Haymie Choi, and Du Toit Loots. 2008. "Effects of dietary onion (Allium cepa L.) in a high-fat diet streptozotocin-induced diabetes rodent model." *Annals of Nutrition and Metabolism* no. 53 (1):6-12.

Jabeen, Bushra, Naheed Riaz, Muhammad Saleem, Muhammad Akram Naveed, Muhammad Ashraf, Umber Alam, Hafiza Mehwish Rafiq, Rasool Bakhsh Tareen, and Abdul Jabbar. 2013. "Isolation of natural compounds from Phlomis stewartii showing α-glucosidase inhibitory activity." *Phytochemistry* no. 96 (0):443-448.

Jaganjac, Morana, O. Tirosh, G. Cohen, S. Sasson, and N. Zarkovic. 2013. "Reactive aldehydes–second messengers of free radicals in diabetes mellitus." *Free radical research* no. 47 (sup1):39-48.

Jaime, A. Y., Connie M. Remsberg, Jody K. Takemoto, Karina R. Vega-Villa, Preston K. Andrews, Casey L. Sayre, Stephanie E. Martinez, and Neal M. Davies. 2013. "Polyphenols and flavonoids: an overview."

Jayaraman, Selvaraj, Anandwardhan A. Hardikar, and A. V. Ramachandran. 2011. "Influence of oreocnide integrifolia (Gaud.) Miq on IRS-1, Akt and Glut-4 in Fat-Fed C57BL/6J type 2 diabetes mouse model." *Evidence-Based Complementary and Alternative Medicine* no. 2011.

Jiang, Baoping, Liang Le, Wenting Wan, Wei Zhai, Keping Hu, Lijia Xu, and Peigen Xiao. 2015. "The flower tea coreopsis tinctoria increases insulin sensitivity and regulates hepatic metabolism in rats fed a high-fat diet." *Endocrinology* no. 156 (6):2006-2018.

Johnson, Anil J., Arun Kumar, Sherin A. Rasheed, Sreeja P. Chandrika, Arun Chandrasekhar, Sabulal Baby, and Appian Subramoniam. 2010. "Antipyretic, analgesic, anti-inflammatory and antioxidant activities of two major chromenes from *Melicope lunu-ankenda*." *Journal of ethnopharmacology* no. 130 (2):267-271.

Kähkönen, Marja P., Anu I. Hopia, Heikki J. Vuorela, Jussi-Pekka Rauha, Kalevi Pihlaja, Tytti S. Kujala, and Marina Heinonen. 1999. "Antioxidant activity of

plant extracts containing phenolic compounds." *Journal of agricultural and food chemistry* no. 47 (10):3954-3962.

Kang, S. J., Lee, J. E., Lee, E. K., Jung, D. H., Song, C. H., Park, S. J., ... & Lee, Y. J. 2014. "Fermentation with Aquilariae Lignum enhances the anti-diabetic activity of green tea in type II diabetic db/db mouse." *Nutrients* no. *6* (9): 3536-3571.

Kassim, Nur Kartinee, Mawardi Rahmani, Amin Ismail, Mohd Aspollah Sukari, Gwendoline Cheng Lian Ee, Nadiah Md Nasir, and Khalijah Awang. 2013. "Antioxidant activity-guided separation of coumarins and lignan from *Melicope glabra (Rutaceae)*." *Food chemistry* no. 139 (1):87-92.

Katsube, Takuya, Naoto Imawaka, Yasuhiro Kawano, Yoshimitsu Yamazaki, Kuninori Shiwaku, and Yosuke Yamane. 2006. "Antioxidant flavonol glycosides in mulberry (Morus alba L.) leaves isolated based on LDL antioxidant activity." *Food Chemistry* no. 97 (1):25-31.

Kaur, Gagandeep, Pradeep Kamboj, and A. N. Kalia. 2011. "Antidiabetic and anti-hypercholesterolemic effects of aerial parts of Sida cordifolia Linn. on Streptozotocin-induced diabetic rats." *Indian J Nat Prod Resour* no. 2 (4):428-434.

Keller, Amy C., Jun Ma, Adam Kavalier, Kan He, Anne-Marie B. Brillantes, and Edward J. Kennelly. 2011. "Saponins from the traditional medicinal plant Momordica charantia stimulate insulin secretion *in vitro*." *Phytomedicine* no. 19 (1):32-37.

Khursheed, RAZIQUE ANWER, TASNEEM FATMA. 2012. "INSULIN LIKE ANTIGEN: SOURCES OTHER THAN PANCREAS." *International Journal of Current Pharmaceutical Research* no. 4 (3):24-28.

Kim, H. K., Y. H. Choi, and R. Verpoorte. 2010. "NMR-based metabolomic analysis of plants." In *Nat Protoc*, 536-49. England.

Kim, Hee-Su, Shin Jung Park, Sun-Hee Hyun, Seung-Ok Yang, Jaehwi Lee, Joong-Hyuck Auh, Jung-Hyun Kim, Soo-Muk Cho, Philip J. Marriott, and Hyung-Kyoon Choi. 2011. "Biochemical monitoring of black raspberry (Rubus coreanus Miquel) fruits according to maturation stage by 1 H NMR using multiple solvent systems." *Food Research International* no. 44 (7):1977-1987.

Klein, Matthias S., and Jane Shearer. 2015. "Metabolomics and Type 2 Diabetes: Translating Basic Research into Clinical Application." *Journal of diabetes research* no. 2016.

Kleinbaum, David G., Lawrence L. Kupper, Keith E. Muller, and Azhar Nizam. 1998. "Applied regression analysis and multivariate methods." *Pacific Grove: Books/Cole*.

Koda, Masanori, Kazuo Furihata, Feifei Wei, Takuya Miyakawa, and Masaru Tanokura. 2012. "Metabolic discrimination of mango juice from various cultivars by band-selective NMR spectroscopy." *Journal of agricultural and food chemistry* no. 60 (5):1158-1166.

Koek, Maud M., Bastiaan Muilwijk, Leo L. P. van Stee, and Thomas Hankemeier. 2008. "Higher mass loadability in comprehensive two-dimensional gas chromatography–mass spectrometry for improved analytical performance in metabolomics analysis." *Journal of Chromatography A* no. 1186 (1):420-429.

Komala, Ismiarni. 2005. "Isolation and Biological Activity of Naturally Occurring Compounds from *Melicope Lunu Ankenda* (Gaertn) T-Hartley, *Melicope* Bonwickii (F-Muell) Tharyley and Tetradium Sambucinum (Bl) Hartley."

Krentz, Andrew J., and Clifford J. Bailey. 2005. "Oral antidiabetic agents." *Drugs* no. 65 (3):385-411.

Kristal, Bruce S., Yevgeniya I. Shurubor, Rima Kaddurah-Daouk, and Wayne R. Matson. 2007. "High-performance liquid chromatography separations coupled with coulometric electrode array detectors." *Metabolomics: Methods and Protocols*:159-174.

Kruit, Janine K., Nadeeja Wijesekara, Jocelyn E. Manning Fox, Xiao-Qing Dai, Liam R. Brunham, Gavin J. Searle, Garry P. Morgan, Adam J. Costin, Renmei Tang, and Alpana Bhattacharjee. 2011. "Islet cholesterol accumulation due to loss of ABCA1 leads to impaired exocytosis of insulin granules." *Diabetes* no. 60 (12):3186-3196.

Kuhl, Carsten, Ralf Tautenhahn, Christoph Bottcher, Tony R. Larson, and Steffen Neumann. 2011. "CAMERA: an integrated strategy for compound spectra extraction and annotation of liquid chromatography/mass spectrometry data sets." *Analytical chemistry* no. 84 (1):283-289.

Kumar, Anoop, Sangeeta Kapoor, and R. C. Gupta. 2013. "Comparison of urinary protein: creatinine index and dipsticks for detection of microproteinuria in diabetes mellitus patients." *Journal of clinical and diagnostic research: JCDR* no. 7 (4):622.

Kvalheim, Olav M., and Terje V. Karstang. 1989. "Interpretation of latent-variable regression models." *Chemometrics and intelligent laboratory systems* no. 7 (1):39-51.

Laakso, M. 2001. "Insulin resistance and its impact on the approach to therapy of type 2 diabetes." *International journal of clinical practice. Supplement* (121):8-12.

Lanza, Ian R., Shucha Zhang, Lawrence E. Ward, Helen Karakelides, Daniel Raftery, and K. Sreekumaran Nair. 2010. "Quantitative metabolomics by H-NMR and LC-MS/MS confirms altered metabolic pathways in diabetes." *PloS one* no. 5 (5):e10538.

Lee, Soo Yee, Ahmed Mediani, Nur Ashikin Ah, Azliana Abu Bakar Sajak, and Faridah Abas. 2014. "Antioxidant and α-glucosidase inhibitory activities of the leaf and stem of selected traditional medicinal plants." *International Food Research Journal* no. 21 (1):165-172.

Lees, Hannah J., Jonathan R. Swann, Ian D. Wilson, Jeremy K. Nicholson, and Elaine Holmes. 2013. "Hippurate: the natural history of a mammalian–microbial cometabolite." *Journal of proteome research* no. 12 (4):1527-1546.

Lenz, Eva Maria, and Ian D. Wilson. 2007. "Analytical strategies in metabonomics." *Journal of proteome research* no. 6 (2):443-458.

Li, Fenglin, Qingwang Li, Dawei Gao, and Yong Peng. 2009. "The optimal extraction parameters and anti-diabetic activity of flavonoids from Ipomoea batatas leaf." *African Journal of Traditional, Complementary and Alternative Medicines* no. 6 (2).

Li, W. L., H. C. Zheng, Joshua Bukuru, and Norbert De Kimpe. 2004. "Natural medicines used in the traditional Chinese medical system for therapy of diabetes mellitus." *Journal of ethnopharmacology* no. 92 (1):1-21.

LI, Y. Q. et al. Comparative evaluation of quercetin, isoquercetin and rutin as inhibitors of α-glucosidase. *Journal of Agricultural and Food Chemistry*, no. 24(57): 11463-11468.

Lima, E. S., and D. S. P. Abdalla. 2001. "Lipid peroxidation: Mechanisms and evaluation in biological samples." *Braz. J. Pharm. Sci* no. 37:293-303.

Lindsay, Robert S., Tohru Funahashi, Robert L. Hanson, Yuji Matsuzawa, Sachiyo Tanaka, P. Antonio Tataranni, William C. Knowler, and Jonathan Krakoff. 2002. "Adiponectin and development of type 2 diabetes in the Pima Indian population." *The Lancet* no. 360 (9326):57-58.

Lisec, Jan, Nicolas Schauer, Joachim Kopka, Lothar Willmitzer, and Alisdair R. Fernie. 2006. "Gas chromatography mass spectrometry–based metabolite profiling in plants." *Nature protocols* no. 1 (1):387-396.

Liu, Haitao, Chongming Wu, Shuai Wang, Shiman Gao, Jiushi Liu, Zhengqi Dong, Bengang Zhang, Mingyue Liu, Xiaobo Sun, and Peng Guo. 2015. "Extracts and lignans of Schisandra chinensis fruit alter lipid and glucose metabolism *in vivo* and *in vitro*." *Journal of Functional Foods* no. 19:296-307.

Liu, Jingping, Chengshi Wang, Fang Liu, Yanrong Lu, and Jingqiu Cheng. 2015. "Metabonomics revealed xanthine oxidase-induced oxidative stress and inflammation in the pathogenesis of diabetic nephropathy." *Analytical and bioanalytical chemistry* no. 407 (9):2569-2579.

Lu, Wenyun, Bryson D. Bennett, and Joshua D. Rabinowitz. 2008. "Analytical strategies for LC–MS-based targeted metabolomics." *Journal of Chromatography B* no. 871 (2):236-242.

Ludwig, Christian, and Mark R. Viant. 2010. "Two-dimensional J-resolved NMR spectroscopy: review of a key methodology in the metabolomics toolbox." *Phytochemical Analysis* no. 21 (1):22-32.

Lynn, Ke-Shiuan, Mei-Ling Cheng, Yet-Ran Chen, Chin Hsu, Ann Chen, T. Mamie Lih, Hui-Yin Chang, Ching-jang Huang, Ming-Shi Shiao, and Wen-Harn Pan. 2015. "Metabolite identification for mass spectrometry-based metabolomics using multiple types of correlated ion information." *Analytical chemistry* no. 87 (4):2143-2151.

Madhujith, Terrence, and Fereidoon Shahidi. 2006. "Optimization of the extraction of antioxidative constituents of six barley cultivars and their antioxidant properties." *Journal of agricultural and food chemistry* no. 54 (21):8048-8057.

Mae, Tatsumasa, Hideyuki Kishida, Tozo Nishiyama, Misuzu Tsukagawa, Eisaku Konishi, Minpei Kuroda, Yoshihiro Mimaki, Yutaka Sashida, Kazuma Takahashi, and Teruo Kawada. 2003. "A licorice ethanolic extract with peroxisome proliferator-activated receptor-γ ligand-binding activity affects diabetes in KK-Ay mice, abdominal obesity in diet-induced obese C57BL mice and hypertension in spontaneously hypertensive rats." *The Journal of nutrition* no. 133 (11):3369-3377.

Mahrous, Engy A., and Mohamed A. Farag. 2015. "Two dimensional NMR spectroscopic approaches for exploring plant metabolome: A review." *Journal of advanced research* no. 6 (1):3-15.

Manach, Claudine, Jane Hubert, Rafael Llorach, and Augustin Scalbert. 2009. "The complex links between dietary phytochemicals and human health deciphered by metabolomics." *Molecular nutrition & food research* no. 53 (10):1303-1315.

Manach, Claudine, Augustin Scalbert, Christine Morand, Christian Rémésy, and Liliana Jiménez. 2004. "Polyphenols: food sources and bioavailability." *The American journal of clinical nutrition* no. 79 (5):727-747.

Mansuri, Mushirbhai Inayatbhai. 2014. "Evaluation of antidiabetic and antihyperlipidemic activity of euphorbia neriifolia linn. in animal models."

Manya, Kiran, Bernard Champion, and Trisha Dunning. 2012. "The use of complementary and alternative medicine among people living with diabetes in Sydney." *BMC complementary and alternative medicine* no. 12 (1):1.

Maritim, A. C., aRA Sanders, and rd J. B. Watkins. 2003. "Diabetes, oxidative stress, and antioxidants: a review." *Journal of biochemical and molecular toxicology* no. 17 (1):24-38.

Matough, Fatmah A., Siti B. Budin, Zariyantey A. Hamid, Nasar Alwahaibi, and Jamaludin Mohamed. 2012. "The role of oxidative stress and antioxidants in diabetic complications." *Sultan Qaboos University Medical Journal* no. 12 (1):5.

Mediani, Ahmed, Faridah Abas, Tan Chin Ping, Alfi Khatib, and Nordin H. Lajis. 2012. "Influence of growth stage and season on the antioxidant constituents of Cosmos caudatus." *Plant foods for human nutrition* no. 67 (4):344-350.

Mhammad, Husni Abdulla, Amad M. Saleh Jubrail, and Malika Kassim Najeeb. 2015. "Impact of Cinnamon Extract on Liver, Kidneys and Spleen of Diabetic Rats." *International Journal of Chemical and Biomolecular Science* no. 4 (1): 248-254

Michiels, Carine, Martine Raes, Olivier Toussaint, and José Remacle. 1994. "Importance of Se-glutathione peroxidase, catalase, and Cu/Zn-SOD for cell

survival against oxidative stress." *Free radical Biology and medicine* no. 17 (3):235-248.

Michl, Johanna, Geoffrey C. Kite, Stefan Wanke, Oliver Zierau, Guenter Vollmer, Christoph Neinhuis, Monique S. J. Simmonds, and Michael Heinrich. 2015. "LC-MS-and 1H NMR-Based Metabolomic Analysis and *in Vitro* Toxicological Assessment of 43 Aristolochia Species." *Journal of natural products*.

Mokiran, Nurul Nadirah, Amin Ismail, Azrina Azlan, Muhajir Hamid, and Fouad Abdulrahman Hassan. 2014. "Effect of dabai (Canarium odontophyllum) fruit extract on biochemical parameters of induced obese–diabetic rats." *Journal of Functional Foods* no. 8:139-149.

Moolla, A., S. F. Van Vuuren, R. L. Van Zyl, and A. M. Viljoen. 2007. "Biological activity and toxicity profile of 17 Agathosma (Rutaceae) species." *South African Journal of Botany* no. 73 (4):588-592.

Motshakeri, Mahsa, Mahdi Ebrahimi, Yong Meng Goh, Hemn Hassan Othman, Mohd Hair-Bejo, and Suhaila Mohamed. 2014. "Effects of brown seaweed (Sargassum polycystum) extracts on kidney, liver, and pancreas of type 2 diabetic rat model." *Evidence-Based Complementary and Alternative Medicine* no. 2014.

Mousinho, Nuno M. H. Da Costa, Jacob J. van Tonder, and Vanessa Steenkamp. 2013. "*In vitro* anti-diabetic activity of Sclerocarya birrea and Ziziphus mucronata." *Natural product communications* (8):1279-84.

Mukherjee, Pulok K., Kuntal Maiti, Kakali Mukherjee, and Peter J. Houghton. 2006. "Leads from Indian medicinal plants with hypoglycemic potentials." *Journal of Ethnopharmacology* no. 106 (1):1-28.

Muranyi, Marianna, Chaonan Ding, QingPing He, Yanling Lin, and Ping-An Li. 2006. "Streptozotocin-induced diabetes causes astrocyte death after ischemia and reperfusion injury." *Diabetes* no. 55 (2):349-355.

Mustafa, R. A., A. Abdul Hamid, S. Mohamed, and F. A. Bakar. 2010. "Total phenolic compounds, flavonoids, and radical scavenging activity of 21 selected tropical plants." In *J Food Sci*, C28-35. United States.

Nelson, D. L., and M. M. Cox. 2000. "Carbohydrates and glycobiology." *Leninger principles of biochemistry, 3rd edn. Worth publishers, New York*:311-318.

Nicholson, Jeremy K., John Connelly, John C. Lindon, and Elaine Holmes. 2002. "Metabonomics: a platform for studying drug toxicity and gene function." *Nature reviews Drug discovery* no. 1 (2):153-161.

Nishigaki, Ikuo, Masako Hagihara, Hiroshi Tsunekawa, Mitsuaki Maseki, and Kunio Yagi. 1981. "Lipid peroxide levels of serum lipoprotein fractions of diabetic patients." *Biochemical medicine* no. 25 (3):373-378.

Noble, Janelle A., and Henry A. Erlich. 2012. "Genetics of type 1 diabetes." *Cold Spring Harbor perspectives in medicine* no. 2 (1):a007732.

Novoa-Carballal, Ramon, Eduardo Fernandez-Megia, Carlos Jimenez, and Ricardo Riguera. 2011. "NMR methods for unravelling the spectra of complex mixtures." *Natural product reports* no. 28 (1):78-98.

Ohkita, Mamoru, Yoshinobu Kiso, and Yasuo Matsumura. 2011. "Pharmacology in health foods: improvement of vascular endothelial function by French maritime pine bark extract (Flavangenol)." *Journal of pharmacological sciences* no. 115 (4):461-465.

Omotayo, Erejuwa O., Sunil Gurtu, Siti Amrah Sulaiman, Mohd Suhaimi Ab Wahab, K. N. S. Sirajudeen, and Md Salzihan Md Salleh. 2010. "Hypoglycemic and antioxidant effects of honey supplementation in streptozotocin-induced diabetic rats." *International Journal for Vitamin and Nutrition Research* no. 80 (1):74.

Othman, Azizah, Nor Juwariah Mukhtar, Nurul Syakirin Ismail, and Sui Kiat Chang. 2014. "Phenolics, flavonoids content and antioxidant activities of 4 Malaysian herbal plants." *International Food Research Journal* no. 21 (2):759-766.

Pan, Zhengzheng, and Daniel Raftery. 2007. "Comparing and combining NMR spectroscopy and mass spectrometry in metabolomics." *Analytical and bioanalytical chemistry* no. 387 (2):525-527.

Parsons, Ian C., Alexander I. Gray, Thomas G. Hartley, and Peter G. Waterman. 1994. "Acetophenones and coumarins from stem bark and leaves of *Melicope stipitata*." *Phytochemistry* no. 37 (2):565-570.

Pasaoglu, Hatice, Banu Sancak, and Neslihan Bukan. 2004. "Lipid peroxidation and resistance to oxidation in patients with type 2 diabetes mellitus." *The Tohoku journal of experimental medicine* no. 203 (3):211-218.

Patel, D. K., S. K. Prasad, R. Kumar, and S. Hemalatha. 2012. "An overview on antidiabetic medicinal plants having insulin mimetic property." *Asian Pacific journal of tropical biomedicine* no. 2 (4):320-330.

Patel, Hemang, Juan Chen, Kumuda C. Das, and Mahendra Kavdia. 2013. "Hyperglycemia induces differential change in oxidative stress at gene expression and functional levels in HUVEC and HMVEC." *Cardiovasc Diabetol* no. 12 (1):142.

Pedersen, Terje R. 2001. "Pro and con: low-density lipoprotein cholesterol lowering is and will be the key to the future of lipid management." *The American journal of cardiology* no. 87 (5):8-12.

Perez-Matute, Patricia, M. Angeles Zulet, and J. Alfredo Mart ńez. 2009. "Reactive species and diabetes: counteracting oxidative stress to improve health." *Current opinion in pharmacology* no. 9 (6):771-779.

Petti, Stefano, and Crispian Scully. 2009. "Polyphenols, oral health and disease: A review." *Journal of dentistry* no. 37 (6):413-423.

Pieczenik, Steve R., and John Neustadt. 2007. "Mitochondrial dysfunction and molecular pathways of disease." *Experimental and molecular pathology* no. 83 (1):84-92.

Pierce, Karisa M., Jamin C. Hoggard, Rachel E. Mohler, and Robert E. Synovec. 2008. "Recent advancements in comprehensive two-dimensional separations with chemometrics." *Journal of chromatography A* no. 1184 (1):341-352.

Poitout, Vincent, Julie Amyot, Meriem Semache, Bader Zarrouki, Derek Hagman, and Ghislaine Fontés. 2010. "Glucolipotoxicity of the pancreatic beta cell." *Biochimica et Biophysica Acta (BBA)-Molecular and Cell Biology of Lipids* no. 1801 (3):289-298.

Porter, Yvette. 2012. "Antioxidant properties of green broccoli and purple-sprouting broccoli under different cooking conditions." *Bioscience Horizons* no. 5:hzs004.

Prabhakar, Pranav Kumar, and Mukesh Doble. 2011. "Mechanism of action of natural products used in the treatment of diabetes mellitus." *Chinese journal of integrative medicine* no. 17 (8):563-574.

Prentki, Marc, and Christopher J. Nolan. 2006. "Islet β cell failure in type 2 diabetes." *The Journal of clinical investigation* no. 116 (7):1802-1812.

Prior, Ronald L., Xianli Wu, and Karen Schaich. 2005. "Standardized methods for the determination of antioxidant capacity and phenolics in foods and dietary supplements." *Journal of agricultural and food chemistry* no. 53 (10):4290-4302.

Psychogios, Nikolaos, David D. Hau, Jun Peng, An Chi Guo, Rupasri Mandal, Souhaila Bouatra, Igor Sinelnikov, Ramanarayan Krishnamurthy, Roman Eisner, and Bijaya Gautam. 2011. "The human serum metabolome." *PloS one* no. 6 (2):e16957.

Punithavathi, Vilapakkam Ranganathan, Ponnian Stanely Mainzen Prince, Ramesh Kumar, and Jemmi Selvakumari. 2011. "Antihyperglycaemic, antilipid peroxidative and antioxidant effects of gallic acid on streptozotocin induced diabetic Wistar rats." *European journal of pharmacology* no. 650 (1):465-471.

Rahier, Jacques, Yves Guiot, R. M. Goebbels, Christine Sempoux, and Jean-Claude Henquin. 2008. "Pancreatic β-cell mass in European subjects with type 2 diabetes." *Diabetes, Obesity and Metabolism* no. 10 (s4):32-42.

Ramli, I., N. H. Kamarulzaman, K. Shaari, and G. C. L. Ee*. 2004. "p-O-geranylcoumaric acid from *Melicope lunu-ankenda*." *Natural product research* no. 18 (4):289-294.

Rang, H. P., M. M. Dale, J. M. Ritter, and P. K. Moore. 2003. "Pharmacology, 5'th edition." *Livingstone: Churchill*.

Ramachandran, Vinayagam, and Ramalingam Saravanan. 2013. "Efficacy of asiatic acid, a pentacyclic triterpene on attenuating the key enzymes activities of carbohydrate metabolism in streptozotocin-induced diabetic rats."*Phytomedicine* no. 20.(3): 230-236.

Ravi, Subban, C. T. Sadashiva, T. Tamizmani, T. Balasubramanian, M. Rupeshkumar, and Indira Balachandran. 2008. "*In vitro* glucose uptake by

isolated rat hemi-diaphragm study of Aegle marmelos Correa root." *Bangladesh Journal of Pharmacology* no. 4 (1):65-68.

Raza, Haider, Annie John, and Frank Christopher Howarth. 2013. "Increased metabolic stress in Zucker diabetic fatty rat kidney and pancreas." *Cellular Physiology and Biochemistry* no. 32 (6):1610-1620.

Ribes, G., Y. Sauvaire, C. Da Costa, J. C. Baccou, and M. M. Loubatieres-Mariani. 1986. "Antidiabetic effects of subtractions from fenugreek seeds in diabetic dogs." *Experimental Biology and Medicine* no. 182 (2):159-166.

Rizvi, Syed Ibrahim, and Neetu Mishra. 2013. "Traditional Indian medicines used for the management of diabetes mellitus." *Journal of diabetes research* no. 2013.

Roberts, Lee D., Albert Koulman, and Julian L. Griffin. 2014. "Towards metabolic biomarkers of insulin resistance and type 2 diabetes: progress from the metabolome." *The Lancet Diabetes & Endocrinology* no. 2 (1):65-75.

Roessner, Ute, and Diane M. Beckles. 2009. "Metabolite measurements." In *Plant metabolic networks*, 39-69. Springer.

Salek, Reza M., Mahon L. Maguire, Elizabeth Bentley, Denis V. Rubtsov, Tertius Hough, Michael Cheeseman, D. Nunez, Brian C. Sweatman, John N. Haselden, and R. D. Cox. 2007. "A metabolomic comparison of urinary changes in type 2 diabetes in mouse, rat, and human." *Physiological genomics* no. 29 (2):99-108.

Sandjo, Louis P., Victor Kuete, Rodrigue S. Tchangna, Thomas Efferth, and Bonaventure T. Ngadjui. 2014. "Cytotoxic benzophenanthridine and furoquinoline alkaloids from Zanthoxylum buesgenii (Rutaceae)." *Chemistry Central Journal* no. 8 (1):61.

Sasidharan, S., Y. Chen, D. Saravanan, K. M. Sundram, and L. Yoga Latha. 2011. "Extraction, isolation and characterization of bioactive compounds from plants' extracts." *African Journal of Traditional, Complementary and Alternative Medicines* no. 8 (1).

Sathyadevi, M., E. R. Suchithra, and S. Subramanian. 2014. "Physalis peruviana Linn. Fruit extract improves insulin sensitivity and ameliorates hyperglycemia in high-fat diet low dose STZ-induced type 2 diabetic rats." *J Pharm Res* no. 8 (4):625-32.

Schaffer, Stephen W., Chian Ju Jong, and Mahmood Mozaffari. 2012. "Role of oxidative stress in diabetes-mediated vascular dysfunction: unifying hypothesis of diabetes revisited." *Vascular pharmacology* no. 57 (5):139-149.

Schönfeld, Peter, Dorota Dymkowska, and Lech Wojtczak. 2009. "Acyl-CoA-induced generation of reactive oxygen species in mitochondrial preparations is due to the presence of peroxisomes." *Free Radical Biology and Medicine* no. 47 (5):503-509.

Scott, Lesley J., and Caroline M. Spencer. 2000. "Miglitol." *Drugs* no. 59 (3):521-549.

Selvan, V. T., L. Manikandan, G. P. Senthil Kumar, R. Suresh, B. B. Kakoti, P. Gomathi, D. A. Kumar, P. Saha, M. Gupta, and U. K. Mazumder. 2008. "Antidiabetic and antioxidant effect of methanol extract of Artanema sesamoides in streptatozocin-induced diabetic rats." *International journal of applied research in natural products* no. 1 (1):25-33.

Serkova, Natalie J., Matthew Jackman, Jaimi L. Brown, Tao Liu, Ryutaro Hirose, John P. Roberts, Jacquelyn J. Maher, and Claus U. Niemann. 2006. "Metabolic profiling of livers and blood from obese Zucker rats." *Journal of hepatology* no. 44 (5):956-962.

Sharif, N. W. Muhd, N. A. Mustahil, N. S. Mohd Noor, M. A. Sukari, M. Rahmani, Y. H. Taufiq-Yap, and G. C. L. Ee. 2013. "Cytotoxic constituents of Clausena excavata." *African Journal of Biotechnology* no. 10 (72):16337-16341.

Shikov, Alexander N., Olga N. Pozharitskaya, Valery G. Makarov, Hildebert Wagner, Rob Verpoorte, and Michael Heinrich. 2014. "Medicinal plants of the Russian Pharmacopoeia; their history and applications." *Journal of ethnopharmacology* no. 154 (3):481-536.

Shn Moorthy, N., M. J Ramos, and P. A Fernandes. 2012. "Studies on α-glucosidase inhibitors development: magic molecules for the treatment of carbohydrate mediated diseases." *Mini reviews in medicinal chemistry* no. 12 (8):713-720.

Shuib, Nor Hassifi, Khozirah Shaari, Alfi Khatib, Maulidiani, Ralf Kneer, Seema Zareen, Salahudin Mohd Raof, Nordin Hj. Lajis, and Victor Neto. 2011. "Discrimination of young and mature leaves of *Melicope ptelefolia* using 1H NMR and multivariate data analysis." *Food Chemistry* no. 126 (2):640-645.

Shukla, A., V. Bukhariya, J. Mehta, J. Bajaj, R. Charde, M. Charde, and B. Gandhare. 2011. "Herbal remedies for diabetes: an overview." *International Journal of Biomedical and Advance Research* no. 2 (1):57-68.

Singh, N. S., M. Geetha, P. Amudha, and Avijit Chakraborty. 2010. "Evaluation of anti-diabetic activity of methanol extract of Flacourtia jangomas (Lour) in streptozotocin induced diabetic rats." *International Journal of Pharma and Bio Sciences* no. 1 (3).

Sivitz, William I., and Mark A. Yorek. 2010. "Mitochondrial dysfunction in diabetes: from molecular mechanisms to functional significance and therapeutic opportunities." *Antioxidants & redox signaling* no. 12 (4):537-577.

Skovsø, S., J. Damgaard, J. J. Fels, G. S. Olsen, X. A. Wolf, B. Rolin, and J. J. Holst. 2015. "Effects of insulin therapy on weight gain and fat distribution in the HF/HS-STZ rat model of type 2 diabetes." *International Journal of Obesity*.

Skovsø, Søs. 2014. "Modeling type 2 diabetes in rats using high fat diet and streptozotocin." *Journal of diabetes investigation* no. 5 (4):349-358.

Solanky, Kirty S., Nigel J. C. Bailey, Bridgette M. Beckwith-Hall, Adrienne Davis, Sheila Bingham, Elaine Holmes, Jeremy K. Nicholson, and Aedin Cassidy. 2003. "Application of biofluid 1 H nuclear magnetic resonance-based

metabonomic techniques for the analysis of the biochemical effects of dietary isoflavones on human plasma profile." *Analytical biochemistry* no. 323 (2):197-204.

Somanah, Jhoti, Emmanuel Bourdon, Philippe Rondeau, Theeshan Bahorun, and Okezie I. Aruoma. 2014. "Relationship between fermented papaya preparation supplementation, erythrocyte integrity and antioxidant status in pre-diabetics." *Food and Chemical Toxicology* no. 65:12-17.

Song, Lili, Hongyue Liu, Yan Wang, Yuming Wang, Jinbiao Liu, Zhensheng Zhou, Huilun Chu, Pengwei Zhuang, and Yanjun Zhang.2015. "Application of GC/MS-based metabonomic profiling in studying the therapeutic effects of Huangbai–Zhimu herb-pair (HZ) extract on streptozotocin-induced type 2 diabetes in mice." *Journal of Chromatography* 997: 96-104.

Song, Xingfang, Junsong Wang, Pengran Wang, Na Tian, Minghua Yang, and Lingyi Kong. .2013. "1 H NMR-based metabolomics approach to evaluate the effect of Xue-Fu-Zhu-Yu decoction on hyperlipidemia rats induced by high-fat diet."*Journal of pharmaceutical and biomedical analysis* 78: 202-210.

Soto-Vaca, Adriana, Ashley Gutierrez, Jack N. Losso, Zhimin Xu, and John W. Finley. 2012. "Evolution of phenolic compounds from color and flavor problems to health benefits." *Journal of agricultural and food chemistry* no. 60 (27):6658-6677.

Srinivasan, K., B. Viswanad, Lydia Asrat, C. L. Kaul, and P. Ramarao. 2005. "Combination of high-fat diet-fed and low-dose streptozotocin-treated rat: a model for type 2 diabetes and pharmacological screening." *Pharmacological Research* no. 52 (4):313-320.

Sundaram, Ramalingam, Rajendran Naresh, Palanivelu Shanthi, and Panchanatham Sachdanandam. 2013. "Modulatory effect of green tea extract on hepatic key enzymes of glucose metabolism in streptozotocin and high fat diet induced diabetic rats." *Phytomedicine* no. 20 (7):577-584.

Suzuki, Makoto, Toshiro Watanabe, Asako Miura, Emiko Harashima, Yasue Nakagawa, and Keisuke Tsuji. 2002. "An extraction solvent optimum for analyzing polyphenol contents by Folin-Denis assay." *Journal-Japanese Society of Food Science And Technology* no. 49 (7):507-511.

Tan, Li Ying, Wai-Fong Yin, and Kok-Gan Chan. 2012. "Silencing quorum sensing through extracts of *Melicope lunu-ankenda*." *Sensors* no. 12 (4):4339-4351.

Tan, Min-Jia, Ji-Ming Ye, Nigel Turner, Cordula Hohnen-Behrens, Chang-Qiang Ke, Chun-Ping Tang, Tong Chen, Hans-Christoph Weiss, Ernst-Rudolf Gesing, and Alex Rowland. 2008. "Antidiabetic activities of triterpenoids isolated from bitter melon associated with activation of the AMPK pathway." *Chemistry & biology* no. 15 (3):263-273.

Tang, Huiru, Yulan Wang, Jeremy K. Nicholson, and John C. Lindon. 2004. "Use of relaxation-edited one-dimensional and two dimensional nuclear magnetic resonance spectroscopy to improve detection of small metabolites in blood plasma." *Analytical biochemistry* no. 325 (2):260-272.

Thoo, Y. Y., S. Y. Ng, M. Z. Khoo, W. M. Wan Aida, and C. W. Ho. 2013. "A binary solvent extraction system for phenolic antioxidants and its application to the estimation of antioxidant capacity in Andrographis paniculata extracts." *International Food Research Journal* no. 20 (3):1103-1111.

Tian, Na, Junsong Wang, Pengran Wang, Xingfang Song, Minghua Yang, and Lingyi Kong. 2013. "NMR-based metabonomic study of Chinese medicine Gegen Qinlian Decoction as an effective treatment for type 2 diabetes in rats." *Metabolomics* no. 9 (6):1228-1242.

Timbrell, John A. 1998. "Biomarkers in toxicology." *Toxicology* no. 129 (1):1-12.

Tiwari, Brahm Kumar, Kanti Bhooshan Pandey, A. B. Abidi, and Syed Ibrahim Rizvi. 2013. "Markers of oxidative stress during diabetes mellitus." *Journal of biomarkers* no. 2013.

Tsutsumi, Yasuhiro, Tsuneo Deguchi, Mikihisa Takano, Akira Takadate, W. Edward Lindup, and Masaki Otagiri. 2002. "Renal disposition of a furan dicarboxylic acid and other uremic toxins in the rat." *Journal of Pharmacology and Experimental Therapeutics* no. 303 (2):880-887.

Tundis, R., M. R. Loizzo, and F. Menichini. 2010. "Natural products as α-amylase and α-glucosidase inhibitors and their hypoglycaemic potential in the treatment of diabetes: an update." *Mini reviews in medicinal chemistry* no. 10 (4):315-331.

Ugarte, Marta, Marie Brown, Katherine A. Hollywood, Garth J. Cooper, Paul N. Bishop, and Warwick B. Dunn. 2012. "Metabolomic analysis of rat serum in streptozotocin-induced diabetes and after treatment with oral triethylenetetramine (TETA)." *Genome Med* no. 4 (4):35.

Vassort, Guy, and Belma Turan. 2010. "Protective role of antioxidants in diabetes-induced cardiac dysfunction." *Cardiovascular toxicology* no. 10 (2):73-86.

Vats, V., S. P. Yadav, and J. K. Grover. 2003. "Effect of T. foenumgraecum on glycogen content of tissues and the key enzymes of carbohydrate metabolism." *Journal of ethnopharmacology* no. 85 (2):237-242.

Viant, Mark R. 2003. "Improved methods for the acquisition and interpretation of NMR metabolomic data." *Biochemical and biophysical research communications* no. 310 (3):943-948.

Virdi, Jaspreet, S. Sivakami, S. Shahani, A. C. Suthar, M. M. Banavalikar, and M. K. Biyani. 2003. "Antihyperglycemic effects of three extracts from Momordica charantia." *Journal of Ethnopharmacology* no. 88 (1):107-111.

Vivekanadan-Giri, Anuradha, Jeffrey H. Wang, Jaeman Byun, and Subramaniam Pennathur. 2008. "Mass spectrometric quantification of amino acid oxidation products identifies oxidative mechanisms of diabetic end-organ damage." *Reviews in Endocrine and Metabolic Disorders* no. 9 (4):275-287.

Wachters-Hagedoorn, R. E., M. G. Priebe, J. A. J. Heimweg, A. M. Heiner, H. Elzinga, F. Stellaard, and R. J. Vonk. 2007. "Low-dose acarbose does not delay digestion of starch but reduces its bioavailability." *Diabetic medicine* no. 24 (6):600-606.

Walford, Geoffrey A., Bianca C. Porneala, Marco Dauriz, Jason L. Vassy, Susan Cheng, Eugene P. Rhee, Thomas J. Wang, James B. Meigs, Robert E. Gerszten, and Jose C. Florez. 2014. "Metabolite traits and genetic risk provide complementary information for the prediction of future type 2 diabetes." *Diabetes care* no. 37 (9):2508-2514.

Wang, Chang, Hongwei Kong, Yufeng Guan, Jun Yang, Jianren Gu, Shengli Yang, and Guowang Xu. 2005. "Plasma phospholipid metabolic profiling and biomarkers of type 2 diabetes mellitus based on high-performance liquid chromatography/electrospray mass spectrometry and multivariate statistical analysis." *Analytical chemistry* no. 77 (13):4108-4116.

Wang, Guo Guang, Xiao Hua Lu, Wei Li, Xue Zhao, and Cui Zhang. 2011. "Protective effects of luteolin on diabetic nephropathy in STZ-induced diabetic rats." *Evidence-Based Complementary and Alternative Medicine* no. 2011.

Wang, Mei, Robert-Jan A. N. Lamers, Henrie A. A. J. Korthout, Joop H. J. van Nesselrooij, Renger F. Witkamp, Rob van der Heijden, Peter J. Voshol, Louis M. Havekes, Rob Verpoorte, and Jan van der Greef. 2005. "Metabolomics in the context of systems biology: bridging traditional Chinese medicine and molecular pharmacology." *Phytotherapy Research* no. 19 (3):173-182.

Wang, Thomas J., Martin G. Larson, Ramachandran S. Vasan, Susan Cheng, Eugene P. Rhee, Elizabeth McCabe, Gregory D. Lewis, Caroline S. Fox, Paul F. Jacques, and Cédine Fernandez. 2011. "Metabolite profiles and the risk of developing diabetes." *Nature medicine* no. 17 (4):448-453.

Wang, Zhijun, Patrick Chan, and Jeffrey Wang. 2013. "Treating type 2 diabetes mellitus with traditional Chinese and Indian medicinal herbs." *Evidence-Based Complementary and Alternative Medicine* no. 2013.

Waters, Nigel J., Catherine J. Waterfield, R. Duncan Farrant, Elaine Holmes, and Jeremy K. Nicholson. 2005. "Metabonomic deconvolution of embedded toxicity: application to thioacetamide hepato-and nephrotoxicity." *Chemical research in toxicology* no. 18 (4):639-654.

Watson, Alison A., George W. J. Fleet, Naoki Asano, Russell J. Molyneux, and Robert J. Nash. 2001. "Polyhydroxylated alkaloids—natural occurrence and therapeutic applications." *Phytochemistry* no. 56 (3):265-295.

Williamson, Gary, and Arianna Carughi. 2010. "Polyphenol content and health benefits of raisins." *Nutrition Research* no. 30 (8):511-519.

Wilson, Ian D., Jeremy K. Nicholson, Jose Castro-Perez, Jennifer H. Granger, Kelly A. Johnson, Brian W. Smith, and Robert S. Plumb. 2005. "High resolution "ultra performance" liquid chromatography coupled to oa-TOF mass spectrometry as a tool for differential metabolic pathway profiling in functional genomic studies." *Journal of proteome research* no. 4 (2):591-598.

Wishart, David S. 2008. "Metabolomics: applications to food science and nutrition research." *Trends in Food Science & Technology* no. 19 (9):482-493.

Wishart, David S. 2011. "Advances in metabolite identification." *Bioanalysis* no. 3 (15):1769-1782.

Wold, Loren E., Asli F. Ceylan-Isik, and Jun Ren. 2005. "Oxidative stress and stress signaling: menace of diabetic cardiomyopathy." *Acta Pharmacologica Sinica* no. 26 (8):908-917.

World Health, Organization. 2006. *Prevention of blindness from diabetes mellitus*: World Health Organization.

Wu, Liang-Yi, Chi-Chang Juan, Low-Tone Ho, Yung-Pei Hsu, and Lucy Sun Hwang. 2004. "Effect of green tea supplementation on insulin sensitivity in Sprague-Dawley rats." *Journal of Agricultural and Food Chemistry* no. 52 (3):643-648.

Wu, Tao, Guoxiang Xie, Yan Ni, Tao Liu, Ming Yang, Huafeng Wei, Wei Jia, and Guang Ji. 2014. "Serum metabolite signatures of type 2 diabetes mellitus complications." *Journal of proteome research* no. 14 (1):447-456.

Wyss, Markus, and Rima Kaddurah-Daouk. 2000. "Creatine and creatinine metabolism." *Physiological reviews* no. 80 (3):1107-1213.

Xia, Jianguo, Trent C. Bjorndahl, Peter Tang, and David S. Wishart. 2008. "MetaboMiner–semi-automated identification of metabolites from 2D NMR spectra of complex biofluids." *BMC bioinformatics* no. 9 (1):1.

Xia, Jianguo, David I. Broadhurst, Michael Wilson, and David S. Wishart. 2013. "Translational biomarker discovery in clinical metabolomics: an introductory tutorial." *Metabolomics* no. 9 (2):280-299.

Xu, Yizhen, Zhiheng He, and George L. King. 2005. "Introduction of hyperglycemia and dyslipidemia in the pathogenesis of diabetic vascular complications." *Current diabetes reports* no. 5 (2):91-97.

Yang, J. H., B. Y. Shin, J. Y. Han, M. G. Kim, J. E. Wi, Y. W. Kim, I. J. Cho, S. C. Kim, S. M. Shin, and S. H. Ki. 2014. "Isorhamnetin protects against oxidative stress by activating Nrf2 and inducing the expression of its target genes." *Toxicol Appl Pharmacol* no. 274 (2):293-301. doi: 10.1016/j.taap.2013.10.026.

YlÄ-Herttuala, Seppo. 1999. "Oxidized LDL and Atherogenesisa." *Annals of the New York Academy of Sciences* no. 874 (1):134-137.

Yokozawa, T., H. Y. Kim, E. J. Cho, J. S. Choi, and H. Y. Chung. 2002. "Antioxidant effects of isorhamnetin 3,7-di-O-beta-D-glucopyranoside isolated from mustard leaf (Brassica juncea) in rats with streptozotocin-induced diabetes." In *J Agric Food Chem*, 5490-5.

Yuan, Wei, Junxiang Zhang §, Shuwei Li, and James L. Edwards. 2011. "Amine metabolomics of hyperglycemic endothelial cells using capillary LC–MS with isobaric tagging." *Journal of proteome research* no. 10 (11):5242-5250.

Yuliana, Nancy Dewi, Alfi Khatib, Young Hae Choi, and Robert Verpoorte. 2011. "Metabolomics for bioactivity assessment of natural products." *Phytotherapy research* no. 25 (2):157-169.

Zhang, Chang-Hua, Guo-Liang Xu, Yu-Hui Liu, Yi Rao, Ri-Yue Yu, Zhong-Wei Zhang, Yue-Sheng Wang, and Liang Tao. 2013. "Anti-diabetic activities of Gegen Qinlian Decoction in high-fat diet combined with streptozotocin-induced diabetic rats and in 3T3-L1 adipocytes." *Phytomedicine* no. 20 (3):221-229.

Zhang, Ming, Xiao-Yan Lv, Jing Li, Zhi-Gang Xu, and Li Chen. 2009. "The characterization of high-fat diet and multiple low-dose streptozotocin induced type 2 diabetes rat model." *Experimental Diabetes Research* no. 2008.

Zhang, Shucha, G. A. Nagana Gowda, Vincent Asiago, Narasimhamurthy Shanaiah, Coral Barbas, and Daniel Raftery. 2008. "Correlative and quantitative 1 H NMR-based metabolomics reveals specific metabolic pathway disturbances in diabetic rats." *Analytical biochemistry* no. 383 (1):76-84.

Zhang, Y. N., M. Li, W. L. Guo, Q. S. Yang, and Z. S. Feng. 2007. "Study on extracting procedure of total flavonoids from Sea-buckthorn." *Academic Periodical of Farm Products Processing* no. 100:8-11.

Zhao, Liangcai, Hongchang Gao, Yongxiang Zhao, and Donghai Lin. 2012. "Metabonomic analysis of the therapeutic effect of Zhibai Dihuang Pill in treatment of streptozotocin-induced diabetic nephropathy." *Journal of ethnopharmacology* no. 142 (3):647-656.

Zhao, Liangcai, Xia Liu, Liyun Xie, Hongchang Gao, and Donghai Lin. 2010. "1H NMR-based metabonomic analysis of metabolic changes in streptozotocin-induced diabetic rats." *Analytical Sciences* no. 26 (12):1277-1282.

Zhao, Qi, Kinzo Matsumoto, Koichi Tsuneyama, Ken Tanaka, Feng Li, Naotoshi Shibahara, Takeshi Miyata, and Takako Yokozawa. 2011. "Diabetes-induced central cholinergic neuronal loss and cognitive deficit are attenuated by tacrine and a Chinese herbal prescription, kangen-karyu: elucidation in type 2 diabetes db/db mice." *Journal of pharmacological sciences* no. 117 (4):230-242.

Zhou, Bin, Jun Feng Xiao, Leepika Tuli, and Habtom W. Ressom. 2012. "LC-MS-based metabolomics." *Molecular BioSystems* no. 8 (2):470-481.

Zia, Tayyaba, S. Nazrul Hasnain, and S. K. Hasan. 2001. "Evaluation of the oral hypoglycaemic effect of Trigonella foenum-graecum L.(methi) in normal mice." *Journal of Ethnopharmacology* no. 75 (2):191-195.

Zuckerman, Jack M., and Dean G. Assimos. 2009. "Hypocitraturia: pathophysiology and medical management." *Rev Urol* no.11 (3): 134-144.