



UNIVERSITI PUTRA MALAYSIA

***ERGOGENIC AND METABOLITES ANALYSES OF PIYAROM DATE
(Phoenix dactylifera L.) USING NMR-BASED METABOLOMICS AND ITS
EFFECT ON SPRAGUE DAWLEY RATS***

HANA KADUM SHANAN

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By

HANA KADUM SHANAN

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

July 2018

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DEDICATION

This thesis is dedicated to my parents, 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

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July 2018

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

People with fatigue need to enhance their energy production and reduce oxidative stress-associated fatigue. In this study, ergogenic activity of different varieties of date (*Phoenix dactylifera* L.) was evaluated using both *in vitro* and *in vivo* study. Selection of the best date variety was based on the ergogenic attributes by antioxidant activity and chemical compositions. The bioactivity of the date fruits (Ajwa, Anbara, Rabbi, Piyarom and Deglet Nour) were evaluated by antioxidant assays, while proton nuclear magnetic resonance ¹H-NMR was used to profile the metabolites of the dates. Ergogenic properties of the date was evaluated *in vivo*, using Sprague dawley rat model. Piyarom extract showed the highest total phenolics content (355 mg GAE/g DW), total flavonoids content (57.07 mg/100g DW), scavenging activity (IC₅₀ of 16.2 µg/mL), ferric reducing antioxidant power (26.38 Mm Fe (II)/g), and strong antioxidant capacity (IC₅₀ 11.3 µg/mL). All the dates have high sugar content that is consistent with their ergogenic attributes electrolyte content of dates (potassium, sodium, magnesium, and calcium) were present in all the dates in substantial amounts. The principal component analysis (PCA) and partial least square discriminate analysis (PLS-DA) plots of different date varieties exhibited clear and distinct separations between the dates. The metabolites identified which may have contributed to the separation were sucrose, betaine, ascorbic acid, fructose, glycine, and arginine. The ergogenic effect of Piyarom extract was then evaluated on fatigue rats. Results of *in vivo* study showed that rats treated with 500 mg/kg BW Piyarom date extract demonstrated the longest endurance capacity of 10 min, that is significantly higher than that of caffeine-treated rats, as measured by forced swimming test. The rats were also found to have normal blood glucose and lactate level after treatment and the values were 5.83 ± 0.64 mmol/L, 10.75 ± 0.89 mmol/L respectively. In addition, serum LDH and creatinine kinase activity (muscle injury indicators) were found to be low 297 ± 29.21 U/L, 749.17 ± 139.40 U/L respectively, in the rats treated with the high

dose date extract, suggesting that energy metabolism was more effective in these rats. In NMR-based on metabolomics data, OPLS-DA showed clear distinct separation between treated and fatigue group's treatment. Furthermore, the OPLS-DA plots showed that metabolites of the rats fed of high dose of date extract were very similar to that of normal rats, which was not obvious in rats treated with the low dose of the extract or that of caffeine. Based on the metabolite identify a clear understanding regarding the underlying mechanism of ergogenic effect of Piyarom date fruit can be elucidation. In conclusion, improvements were seen in rats treated with high dose Piyarom date extract in terms of endurance capacity, energy metabolism, muscle injury parameters and metabolites generated that are not seen in the rats treated with caffeine. Date fruit can thus be used as an ingredient in the development of functional foods (drinks or snacks) with ergogenic property. The product will be exceptionally useful for fatigue and normal individuals who desire a more active and healthier lifestyle without the oxidative stress associated lethargy.

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

**ANALISIS ERGOGENIK DAN METABOLITS DARIPADA BUAH
PIYAROM KURMA (*Phoenix dactylifera* L.) MELALUI METABOLOMIK
YANG BERASASKAN NMR DAN KESAN PADA TIKUS SPRAGUE
DAWLEY**

Oleh

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Orang yang letih perlu meningkatkan pengeluaran tenaga dan mengurangkan keletihan yang berkaitan dengan tekanan oksidatif. Dalam kajian ini, aktiviti ergogenik dari pelbagai jenis buah kurma (*Phoenix dactylifera* L.) telah dikaji dengan menggunakan kedua-dua kajian *in vitro* dan *in vivo*. Pemilihan variety buah kurma yang terbaik adalah berdasarkan sifat-sifat ergogenic daripada aktiviti antioksidan dan komposisi kimia. Bioaktiviti buah-buahan kurma (Ajwa, Anbara, Rabbi, Piyarom dan Deglet Nour) telah dinilai dengan ujian antioxidant, manakala resonans magnetic nuclear proton $^1\text{H-NMR}$ digunakan untuk memaparkan metabolit bioaktif buah kurma, dan seterusnya sifat ergogenic telah ditentukan *in vivo* menggunakan model tikus Sprague Dawley. Satu kajian diskriminasi mengenai metabolit yang bertanggungjawab terhadap variasi antara sampel telah dilakukan dengan menggunakan metabolomik berasaskan $^1\text{H-NMR}$. Ekstrak Piyarom menunjukkan kandungan yang tertinggi bagi jumlah fenolik (355 mg GAE/g DW), dan jumlah flavonoid (57.07 mg/100g DW), aktiviti penipisan (IC_{50} of 16.2 $\mu\text{g/mL}$), Ferric pengurangan kuasa antioksida (26.38 Mm Fe (II)/g) dan keupayaan antioksidan (IC_{50} 11.3 $\mu\text{g/mL}$). Semua buah kurma mempunyai kandungan gula yang tinggi dan hasil kajian ini adalah konsisten dengan sifat ergogenic elektrolit buah kurma (potassium, natrium, magnesium dan kalsium) yang berada dalam semua kurma dalam jumlah yang banyak. Plot PCA (*principal component analysis*) dan PLS-DA (*partial least square discriminate analysis*) bagi buah kurma yang berbeza mempamerkan pemisahan yang jelas dan berbeza antara buah-buahan kurma. Metabolit yang dikenalpasti kemungkinan menyumbang kepada pemisahan itu ialah sukrosa, betaine, asid askorbik, fruktosa, glisin, dan arginine. Kesan ergogenic dari ekstrak Piyarom kemudiannya dinilai pada tikus yang letih. Hasil kajian *in vivo* menunjukkan bahawa tikus dirawat dengan 500 mg/kg BW ekstrak Piyarom buah kurma menunjukkan daya

tahan terpanjang selama 10 menit, hasil kajian ini jauh lebih tinggi daripada tikus yang dikendalikan dengan kafein, seperti yang diukur dengan ujian berenang paksa. Tikus-tikus ini juga didapati mempunyai tahap glukosa dan taktat darah yang biasa selepas rawatan dan jumlah bacaan tersebut masing-masing adalah 5.83 ± 0.64 mmol/L, 10.75 ± 0.89 mmol/L. Selain itu, aktiviti LDH dan creatinine kinase serum (petunjuk kecederaan otot) didapati paling rendah dalam tikus yang dirawat dengan buah kurma dos yang tinggi, masing masing 297 ± 29.21 U/L, 749.17 ± 139.40 U/L, menunjukkan bahawa metabolisma tenaga lebih berkesan dalam tikus ini, Dalam metabolom berasaskan NMR data, OPLS-DA menunjukkan pemisahan yang jelas antara rawatan bagi kumpulan keletihan dan kumpulan yang dirawat. Selain itu, plot OPLS-DA menunjukkan bahawa metabolit tikus yang diberi makan ekstrak dos tinggi sangat serupa dengan tikus yang biasa, manakala tidak jelas pada tikus yang dirawat dengan dos rendah ekstrak atau kafein. Berdasarkan metabolit, pengenalan pemahaman yang jelas mengenai mekanisme kesan ergogen yang mendasari buah kurma Piyarom dapat dijelaskan. Kesimpulannya, penambahbaikan dilihat pada tikus yang dirawat dengan ekstrak dosis tinggi piyarom dari segi keupayaan ketahanan, metabolisma tenaga, parameter kecederaan otot dan metabolit yang dihasilkan yang tidak dapat dilihat dalam tikus yang dirawat dengan kafein. Buah kurma boleh digunakan sebagai ramuan dalam pembuatan makanan berfungsi (minuman atau makanan ringan) dengan ergogenik. Produk ini akan berguna bagi individu yang sering mengalami keletihan dan individu yang menginginkan gaya hidup yang lebih aktif dan sihat tanpa tekanan oksidatif yang berkaitan dengan kelesuan.

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

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TABLE OF CONTENTS

	Page
ABSTRACT	i
ABSTRAK	iii
ACKNOWLEDGEMENTS	v
APPROVAL	vi
DECLARATION	viii
LIST OF TABLES	xiv
LIST OF FIGURES	xv
LIST OF ABBREVIATIONS	xx
CHAPTER	
1 INTRODUCTION	1
1.1 Background of the Study	1
1.2 Problem Statement	3
1.3 Research Objectives	3
2 LITERATURE REVIEW	5
2.1 Ergogenic activity	5
2.1.1 Ergogenic Aids	5
2.1.2 Supplements as ergogenic aides	6
2.1.2.1 Antioxidants (vitamin C, vitamin E, and coenzyme Q10)	6
2.1.2.2 Arginine	7
2.1.2.3 Beet root or beet juice	7
2.1.2.4 Beta-alanine	8
2.1.2.5 Beta-hydroxyl-beta-methyl butyrate (HMB)	8
2.1.2.6 Caffeine	8
2.1.2.7 Creatine	8
2.1.2.8 Ginseng	9
2.1.3 Sport and energy drinks	9
2.1.4 Mechanisms of ergogenic substances in natural plants	10
2.1.5 Phytochemicals as ergogenic aids	10
2.1.6 Ergogenic properties of bio-active compounds	11
2.1.7 Ergogenic properties of fruits	12
2.2 Date palm (Phoenix dactylifera L.)	13
2.2.1 Date varieties of the world	14
2.2.2 Chemical composition of date fruit	15
2.2.2.1 Sugar content	15
2.2.2.2 Mineral contents of date fruit	17
2.2.2.3 Proteins and fats	18
2.2.2.4 Vitamin content	19
2.2.2.5 Moisture content and crude fibres (non-soluble solids)	19

2.2.3	Antioxidant	20
2.2.4	Biological and medicinal values of dates	21
2.3	Metabolomics	22
2.3.1	Applications of metabolomics	23
2.3.2	Metabolomics and its clinical applications	23
2.3.3	Analytical techniques for metabolomics	25
2.3.3.1	Nuclear magnetic resonance (NMR) spectroscopy	25
2.3.3.2	Mass Spectrometry (MS)	26
2.3.3.3	Gas Chromatography-Mass Spectroscopy (GC-MS)	27
2.3.3.4	Liquid chromatography-mass spectrometry (LC-MS)	27
2.3.4	Data processing and statistical analysis in metabolomics	28
2.3.4.1	Principal component analysis (PCA)	28
2.3.4.2	Partial least square (PLS)	29
2.3.4.3	Partial least square discriminate analysis (PLS-DA)	29
3	PROXIMATE ANALYSIS AND ANTIOXIDANT ACTIVITY OF DIFFERENT VARIETIES OF DATES (<i>Phoenix dactylifera</i> L.)	30
3.1	Introduction	30
3.2	Methods and Materials	30
3.2.1	Chemicals and Reagents	30
3.2.2	Plant Materials and Extraction	31
3.2.3	Proximate Analysis	31
3.2.4	Mineral Determination	32
3.2.5	Sugar content	32
3.2.6	Total phenolic compounds (TPC) determination	32
3.2.7	Total Flavonoids Content (TFC) determination	33
3.2.8	Antioxidant assays	33
3.2.8.1	Free Radical Scavenging (DPPH)	33
3.2.8.2	Ferric Reducing Antioxidant Power (FRAP)	33
3.2.8.3	Antioxidant Capacity (ABTS)	34
3.2.9	Statistical Analysis	34
3.3	Results and discussion	34
3.3.1	Percent extraction yield	34
3.3.2	Proximate compositions of dates	35
3.3.3	Mineral Content	37
3.3.4	Sugar Content	39
3.3.5	Total Phenolic Compounds (TPC)	40
3.3.6	Total Flavonoid Content (TFC)	41
3.3.7	Radical Scavenging Activity (DPPH)	43
3.3.8	Ferric Reducing Antioxidant Power (FRAP)	44
3.3.9	Antioxidant Capacity (ABTS)	45
3.4	Conclusion	46

4	METABOLITES PROFILING OF DIFFERENT VARIETIES OF DATE AND CORRELATIONS TO THEIR BIOLOGICAL ACTIVITY USING ¹H-NMR	47
4.1	Introduction	47
4.2	Methods and Materials	48
4.2.1	Chemicals and Reagents	48
4.2.2	Plant Materials and Extraction	48
4.2.3	Proton ¹ H-NMR Measurements	48
4.2.4	Proton ¹ H-NMR spectra bucketing	48
4.2.5	Statistical Analysis	49
4.3	Results and Discussion	49
4.3.1	¹ H-NMR Spectra and Metabolites Identification	49
4.3.2	Multivariate data analysis of different varieties of date extract	59
4.3.3	Relative quantities of metabolites identified	63
4.3.4	Relationship between metabolites and antioxidant activities of different date varieties	65
4.3.5	PLS model validation	66
4.4	Conclusion	68
5	ERGOGENIC EFFECT OF PIYAROM DATE EXTRACT IN FATIGUE SPRAGUE DAWLEY RATS	69
5.1	Introduction	69
5.2	Material and Methods	69
5.2.1	Plant Materials and Extraction	69
5.2.2	<i>In vivo</i> Experimentation	70
5.2.3	Feed and water intake in rats	72
5.2.4	Collection of urine, blood, and, organs	72
5.2.5	Biochemical Analyses	72
5.2.6	Forced swimming test	73
5.2.7	Histological staining of organs	73
5.2.8	Statistical Analysis	73
5.3	Results and Discussion	73
5.3.1	Animal experiment	73
5.3.2	Weight loaded forced swimming test	75
5.3.3	Biochemical parameters related to energy metabolism	78
5.3.3.1	Effect of Piyarom date extract on blood glucose level of the rats.	78
5.3.3.2	Effect of Piyarom Date Extract on blood Lactate level of rats.	80
5.3.3.3	Effect of Piyarom date extract on serum LDH activity of rats	81
5.3.3.4	Effect of Piyarom date extract on blood level of creatine kinase in rats.	82
5.3.3.5	Lipid profile	83
5.3.4	Effects of Piyarom date extract on kidney function test	86
5.3.5	Effects of Piyarom date extract on rat liver function	88
5.3.6	Toxicity indicators of the treatments	89

5.3.7	Histological examinations of heart, kidney, liver and gastrocnemius muscle tissues of rats.	91
5.4	Conclusion	98
6	METABOLITES CHANGES IN EXERCISE INDUCED FATIGUE RATS TREATED WITH PIYAROM DATE FRUIT EXTRACT (<i>Phoenix dactylifera</i> L.) USING ¹H-NMR BASED METABOLOMICS	99
6.1	Introduction	99
6.2	Materials and Methodology	100
6.2.1	Chemicals and reagents	100
6.2.2	Animal study	100
6.2.3	Serum and urine collection	100
6.2.4	¹ H-NMR analysis of urine and serum	101
6.2.5	NMR spectral reduction and multivariate data analysis	101
6.2.6	Statistical analysis	102
6.3	Results and discussion	102
6.3.1	¹ H-NMR Spectra of Serum Metabolites before Treatment	102
6.3.2	Multivariate data analysis of serum samples of fatigue and normal rats	109
6.3.3	Multivariate Data Analysis of serum of All Groups after 8 weeks of Treatment	113
6.3.4	Metabolites analysis of serum NMR data of date extract and caffeine treatments at different period	122
6.3.5	¹ H-NMR Spectra of urine metabolites before treatment	126
6.3.6	Multivariate data analysis of urine samples of fatigue and normal rats	135
6.3.7	Multivariate data analysis of urine NMR data of all groups at week 8 of treatment	138
6.3.8	Metabolites analysis of urine NMR data of date extract and caffeine at different period of treatment	146
6.4	Metabolic alterations of the response to date extract treatment	149
6.4.1	Changes in energy metabolism (TCA)	150
6.4.2	Changes in carbohydrate metabolism	150
6.4.3	Changes in amino acid metabolism	151
6.4.4	Lipid metabolism	151
6.4.5	Changes in the metabolism of additional metabolites	151
6.5	Conclusions	154
7	CONCLUSION AND RECOMMENDATIONS	155
7.1	Summary and Conclusion	155
7.2	Recommendations	156
	REFERENCES	157
	APPENDICES	180
	BIODATA OF STUDENT	194
	LIST OF PUBLICATIONS	195

LIST OF TABLES

Table	Page	
3.1	Percentage yield of different varieties of date	35
3.2	Chemical composition of different date varieties	36
3.3	Mineral content (mg/100g DF) of different varieties of date	38
3.4	Sugar concentration (mg/100g DF) of date varieties	39
4.1	Assignments of ¹ H-NMR spectral signals obtained from different varieties of date fruit	56
4.2	VIP values of the major contributing compounds in the PLS	66
5.1	Blood level of creatine kinase after 8 weeks of treatment	83
5.2	Serum creatinine and urea levels of rats after 8 weeks of treatment with Piyarom date extract	87
5.3	Serum level of ALT, AST and GGT in rats	88
5.4	Weight (g) of body organs of rats after 8 weeks of treatments	90
6.1	Relative quantitative of discriminating metabolites of serum in fatigue rats (FG) and normal rats (NG) before treatment using Chenomx NMR Suite	107
6.2	Relative quantities of significant discriminating metabolites of serum using Chenomx NMR Suite at week 8 of treatment	117
6.3	Relative quantitative of discriminating metabolites of urine of Fatigue rats (FG) and normal rats (NG) before treatment using Chenomx NMR Suite	131
6.4	Relative quantitative of significant discriminating metabolites of urine using Chenomx NMR Suite at week 8 of treatment	141

LIST OF FIGURES

Figure		Page
2.1	Proximate composition of date palm flesh (data is average of 15 varieties of dates; Al-Shahib and Marshall, 2003).	16
3.1	Total phenolic content of extracts of dates	41
3.2	Total flavonoid content of different varieties of date	42
3.3	DPPH Radical scavenging activity of different varieties of date extracts	43
3.4	FRAP Ferric reducing antioxidant power of different varieties of date extracts	44
3.5	ABTS Antioxidant Capacity of different varieties of date extracts	45
4.1	The representative of $^1\text{H-NMR}$ spectra of the five varieties of dates extract	50
4.2	The representative of $^1\text{H-NMR}$ spectra of the five varieties of dates extracts expanded spectra for the range between (δ 1.5 to 3) A, expanded spectra for the range between (δ 3 to 6) B, and expanded spectra for the range between (δ 6 to 8) C	54
4.3	A, B & C- $^1\text{H-}^1\text{H}$ J-resolved spectra of Deglet Nour extract in the region δ 3.0 to 5.5	59
4.4	PCA score plot (PC1 vs. PC2) of the $^1\text{H-NMR}$ the ethanolic extracts of different varieties of date. A, Ajwa: AN, Anbara; R, Rabbi; P, Piyarom; DN, Deglet Nour	60
4.5	The PLS-DA score plot (PC1 vs. PC2 A) and the loading column plots of PC1 (B) and PC2 (C) of the $^1\text{H-NMR}$ the ethanolic extracts of different varieties of date	62
4.6	Relative quantities of the metabolites identified in all five varieties of date extracts based on the mean peak area of the $^1\text{H-NMR}$ signals	64
4.7	The biplot obtained from PLS describing the relation between the metabolites with antioxidant activities in extract of different varieties of date	65
4.8	PLS models validation with 100 permutations of DPPH (A), ABTS (B), and FRAP (C)	68

5.1	Flow chart for experimental design to evaluate the ergogenic effect of date extract in fatigue male Sprague-Dawley rats	71
5.2	Effects of Piyarom extract on food intake of rats	74
5.3	Effects of Piyarom extract on water intake of rats	74
5.4	Effect of Piyarom extract on body weights of rats	75
5.5	Endurance capacity test of rats at the end of 8 weeks treatment	77
5.6	Blood Glucose Level of rats after 8 weeks of treatment	79
5.7	Blood Lactate Level of the rats after 8 weeks of treatment	80
5.8	Serum LDH activity in rats after 8 weeks of treatment	82
5.9	Total cholesterol levels of rats after 8 weeks of treatment	84
5.10	Total Triglycerides levels of rats after 8 weeks of treatment	84
5.11	Total LDL levels of rats after 8 weeks of treatment	85
5.12	HDL levels of rats after 8 weeks of treatment	86
5.13	Effects of the date on the histological appearance of (a) heart, (b) kidney, (C) liver, and (D) Gastrocnemius muscle in rats are shown by photomicrographs. Representative histological sections of the heart, kidney, liver, and Gastrocnemius muscle were stained with haematoxylin and eosin. Specimens were photographed by light microscopy. (H&E stain, magnification: $\times 400$; Scale bar, 50 μm)	97
6.1	A 500 MHz ^1H -NMR spectra of serum collected from normal and fatigue Sprague-Dawley rat before treatment	103
6.2	Typical 500 MHz ^1H NMR serum (A) (0 to 3ppm) and (B) (3 to 6ppm) spectra collected from fatigue rats (FG) and normal rats (NG) before treatment	106
6.3	OPLS-DA score plot (A), loading plot (B) obtained using ^1H -NMR data for serum samples from Sprague-Dawley rats, Fatigue group (FG) and normal group (NG) before treatment	110
6.4	VIP values of serum metabolites responsible for the discrimination between normal and fatigue rats derived from PLS-DA	111
6.5	PCA score plot (A) and OPLS-DA score (B) obtained using ^1H -NMR data for serum samples from fatigue group (FG), caffeine group (CFG), low dose group (LDFG) and high dose group (HDFG) at week 8 of treatment	114

6.6	PCA Loading plot obtained using ¹ H-NMR data for serum samples from fatigue group (FG), caffeine group (CFG), low dose group (LDFG) and high dose group (HDFG) at week8 of treatment	116
6.7	VIP values of serum metabolites responsible for the discrimination between treated and fatigue rats derived from PLS-DA	119
6.8	The box plots of the relative quantities of the most significant metabolites in the serum samples from the treated and untreated groups	121
6.9	OPLS-DA score plot of date extract (A) and caffeine (B) obtained using ¹ H-NMR data for serum samples from fatigue group (FG), week0 (HDFG0 and CFG0), week4 (HDFG4 and CFG) and week8 (HDFG8 and CFG8) of treatment	124
6.10	OPLS-DA loading column plot of date obtained using ¹ H-NMR data for serum samples from rats, Week0 (HDFG0), and Week8 (HDFG8)	125
6.11	OPLS-DA loading column caffeine obtained using ¹ H-NMR data for serum samples from rats, Week0 (CFG0), and Week8 (CFG8)	125
6.12	A Typical 500 MHz ¹ H-NMR urine, B (1 to 3ppm), C (3 to 6ppm), and D (6- to 9ppm) spectra with identified metabolites collected from Fatigue group (FG) and normal group (NG) Sprague Dawley rat	130
6.13	OPLS-DA score plot A, loading plot B, obtained using ¹ H-NMR data for urine samples from Fatigue group (FG) and normal group (NG) before treatment	136
6.14	VIP values of urine metabolites responsible for the discrimination between normal and fatigue rats derived from PLS-DA	137
6.15	PCA score plot (A) and OPLS-DA score (B) obtained using ¹ H-NMR data for urine samples from Sprague-Dawley rats, normal group (NG), caffeine group (CFG), low dose group (LDFG) or high dose group (HDFG) at week8 of treatment	139
6.16	PCA loading plot obtained using ¹ H-NMR data for urine samples from Sprague-Dawley rats, normal group (NG), caffeine group (CFG), low dose group (LDFG) or high dose group (HDFG) at week 8 of treatment	140
6.17	VIP values of urine metabolites responsible for the discrimination between treated and fatigue rats derived from PLS-DA	144
6.18	The box plots of the relative quantities of the most significant metabolites in the urine samples from the treated and untreated groups	145
6.19	OPLS-DA score plots of date (A) and caffeine (B) obtained using ¹ H NMR data for urine samples from Sprague-Dawley rats, normal group	

(NG), week0 (HDFG0 and CFG0), week4 (HDFG4 and CFG4) and week8 (HDFG8 and CFG8)	147
6.20 Loading column plot of date obtained using ¹ H-NMR data for urine samples from Sprague-Dawley rats, week 0 (HDFG0), and week 8 (HDFG8)	148
6.21 Loading column plot of caffeine obtained using ¹ H-NMR data for urine samples from Sprague-Dawley rats, week0 (CFG0), and week8 (CFG8)	149
6.22 Metabolism pathways describing the regulation of potential serum and urine biomarkers upon date extract treatment	153



LIST OF ABBREVIATIONS

$^1\text{H-NMR}$	Proton Nuclear Magnetic Resonance Spectroscopy
<i>d</i>	Doublet
<i>dd</i>	Doublet of doublet
DPPH	Diphenylpicrylhydrazyl
ABTS	2, 2'-azino-bis 3-ethylbenzothiazoline sulphate
FRAP	Ferric reducing antioxidant power
g	Gram
GAE	Gallic Acid Equivalent
Hz	Hertz
hr	hour
IC ₅₀	Inhibition Concentration at 50 percent
L	Litre
m	Multiplet
MHz	Mega Hertz
min	minute
mL	Milliliter
MS	Mass Spectrometry
MVDA	multivariate data analysis
°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
<i>s</i>	Singlet
SIMCA	Soft Independent Modelling of Class Analogy
TPC	Total Phenolic Contents
UV	Ultraviolet
TFC	Total Flavonoid Content

VIP	variable importance in the projection
δ	Chemical Shift in ppm
μg	Microgram
μL	Microliter
^{13}C	Carbon-13
BW	Body weight
DF	Date fruit
TSP	Trimethylsilyl propionic acid -d4 sodium salt
HMBC	Heteronuclear Multiple-Bond Correlation
CMC	Carboxymethyl cellulose



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CHAPTER 1

INTRODUCTION

1.1 Background of the Study

Ergogenic property is defined as the ability of substances to enhance the capacity for physical activities through production of energy, thereby giving an individual a competitive edge in competition and the ability to reduce oxidative stress-associated fatigue. Consequently, there will also be an improvement in the individual's physical well-being (Silver, 2001). The ergogenic effects in most cases involve a reduction in oxidative stress that leads to lowering of inflammatory process and risk of developing chronic diseases (Howatson et al., 2010; Miranda-Vilela et al., 2009; Tartibian & Maleki, 2012).

Currently, there are various types of ergogenic aids available in the market including protein, amino acid (arginine, leucine, L-carnitine), caffeine, guarana, minerals such as calcium, magnesium, sodium, potassium, etc. (Kalman et al., 2012), and herbal extracts like chilli pepper (that contains Capsaicin), Ginkgo biloba, and Ginseng (Chen et al., 2012; Williams, 2006). These compounds are involved in a variety of metabolic reactions in the human body (Apostu, 2014; Volpe, 2008). These aids are normally added into beverages like energy or sports drinks, which are suitable for athletic performance and also a good source of fluid and electrolytes lost in sweat during exercise. Energy drinks are suggested for boosting the body energy, improving concentration of the athlete and decreasing oxidative stress-associated fatigue (Care, 2011). The presence of electrolytes such as sodium, magnesium, and calcium in these beverages will motivate drinking and alleviate thirst sensation instead of plain water for rehydration after exercise (Kalman et al., 2012). Beverages may demonstrate their ergogenic effects by way of increasing muscle mass, decreasing body fat, increasing growth hormone secretion, enhancing strength and power, preventing excessive formation of free radicals and preventing fatigue.

Currently, in the market, there are various types of sports and energy drinks that are popular not only among athletes and active individuals, but also popular with young adults and the elderly. However, over-consumption of these ergogenic aids may result in side effects including allergic reaction of the central nervous system, gastrointestinal, and kidney damage (Aarthi & Persad, 2011; Seifert & Schaechter, 2011).

Great number of studies showed the ergogenic activity of several fruits that enhanced human performance in physical activities. In previous study, watermelon juice consumed by individuals before exercise boosted performance and the author suggested that the activity is due to the presence of several nutrients such as citrulline

and essential amino acid (Tarazona-Diaz, 2013). In another study, Nieman et al. (2012) studied the effects of ingesting bananas in comparison to 6% carbohydrate drink on 75-km cycling performance and post-exercise and found that eating bananas before exercise is an effective strategy to enhance performance of the individuals. Moreover, beetroot and leafy greens vegetables were reported to be good sources of nitrate that is absorbed by the small intestine. The results demonstrated reduction of pulmonary oxygen uptake (VO_2) during submaximal exercise and increase tolerance of high-intensity work rates are due to the presence of nitrate that can be a potent ergogenic aid (Cermak, 2012).

Since time immemorial, the date fruit has constituted a major part of human diet. Middle Eastern populations and Muslims especially, around the world have consumed date fruits because they believed in the health benefits of the fruit as recommended in the Holy Quran (Ismail et al., 2008). In addition, dates are known as important nutritional therapy in different culture and traditions worldwide. The Bible refers to the date palm as the “tree of life” because of its excellent dietetic value, exceptional yields and long shelf life under natural conditions (Al-Farsi and Lee, 2008). There are in excess of 5000 known date varieties available and categorised on the basis of shape, size, location of origin and organoleptic properties of the fruits (Baliga et al., 2011; Rahmani et al., 2014). Some of the important date varieties grown around the world are Ajwa, Anbara, Piyarom, Safawi, and Deglet Nour (Baliga et al., 2011). Individual varieties have their distinctive nutritional value and pharmacological properties, which may be affected by various factors such as genetic makeup and chemical composition.

Earlier research have shown that dates can provide rapid energy to the host due to their high content of sugars, namely glucose, fructose, and sucrose (Ashraf and Esfahani, 2011; Baliga et al., 2011). In addition, dates consist of various minerals such as calcium, copper, iron, magnesium, manganese, potassium, phosphorous, selenium, sodium and zinc (Borchani et al., 2010; Hasnaoui et al., 2012). Some of these minerals are electrolytes known to have ergogenic attributes. In addition, dates have also been reported to possess good antioxidant activity, it can prevent, inhibit or delay oxidation of biomolecules and reduce oxidative stress, consequently, reduce fatigue and aid in free radicals scavenging (Allaith, 2008; Al-Juhaimi et al., 2014; Li, Wong et al., 2008). Studying the ergogenic potential(s) of date fruits in living tissues by $^1\text{H-NMR}$ metabolomics could be a very good approach.

Metabolomics is a tool used to study the metabolome, which consists of the low molecular weight molecules of an organism. It is a robust method for the evaluation of changes in metabolites of the biological system under different conditions. Metabolomics is an efficient profiling tool for the purpose of detecting metabolites and metabolic pathways assessment in the organism and their variations. (Kaddurah-Daou et al., 2008). The combination of $^1\text{H-NMR}$ spectroscopy together with multivariate data analysis (MVDA) has emerged as an efficient tool for not only identifying and discriminating a large number of metabolites but also for improving

the understanding of diseases or disorders through the identification of altered pathways and networks (Cevallos-Cevallos et al., 2009; Meyer et al., 2013).

1.2 Problem Statement

Fatigue is a feeling of extreme physical and mental tiredness. People from all over the world face fatigue due to pressure induced by heavy work, and physical activities, illnesses and excessive oxidative stress that can increase the risk for development of various chronic diseases. It is imperative that these individuals enhance their use and production of energy, thus reduce oxidative stress-associated fatigue and improve their overall healths. This can be achieved by consuming natural foods that have been shown to be effective in improving energy production and fatigue alleviation.

Dates are excellent candidates for this purpose as they contain various nutrients and bioactive compounds with ergogenic attributes. Although, some of the nutritional and biological properties of dates have been reported (Bouhlali et al., 2015; Zahra, Jafar, & Omid, 2015; Al Harthi et al., 2015), the study of its ergogenic properties may not have been reported to the best of our knowledge. Dates as a natural food, can be used as an alternative to the commonly used ergogenic aids that could be detrimental to health when consumed too frequently. However, the date fruits are seasonal and they grow in certain regions in the world which can lead to limited access by large communities around the world. In addition, the date fruits are very rich in nutrients and that makes the fruit targeted by spoilage microorganisms and that will cause economic losses. There are very few studies determined the transformation of date fruits into other forms such as syrups and paste. Nevertheless, extraction of date fruits by suitable solvents can facilitate their applications as bioactive ingredients for functional foods.

1.3 Research Objectives

The overall research objective is to investigate the ergogenic properties of date fruit. The specific objectives are:

- 1 - To determine the chemical compositions and antioxidant activity of different varieties of dates (Ajwa, Anbara, Piyarom, Rabbi, and Deglet Nour) *in vitro*.
- 2 - To profile the metabolites of the dates studied using ¹H-NMR metabolomics analysis.
- 3 - To investigate the ergogenic effect of the best date studied in fatigue-induced Sprague Dawley rats.

4 - To evaluate the ergogenic effect of the dates studied on the metabolic perturbations of fatigue-induced rats through their serum and urine using $^1\text{H-NMR}$ -based metabolomics.



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