UNIVERSITI PUTRA MALAYSIA

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

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By

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

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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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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 ^{1}H-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 (IC_{50} of 16.2 µg/mL), ferric reducing antioxidant power (26.38 Mm Fe (II)/g), and strong antioxidant capacity (IC_{50} 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

HANA KADUM SHANAN

Julai 2018

Pengerusi : Profesor Azizah Abdul Hamid, PhD
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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 1H-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}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 µg/mL), Ferric pengurangan kuasa antioksida (26.38 Mm Fe (II)/g) dan keupayaan antioksidan (IC_{50} 11.3 µg/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-buah 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 minit, 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 bacaaan 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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I certify that a Thesis Examination Committee has met on 30 July 2018 to conduct the final examination of Hana Kadum Shanan on her thesis entitled "Ergogenic and Metabolites Analyses of Piyarom Date (*Phoenix dactylifera* L.) Using NMR-Based Metabolomics and its Effect on Sprague Dawley Rats" 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.

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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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Declaration by Members of Supervisory Committee

This is to confirm that:

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LIST OF ABBREVIATIONS

^{1}H-NMR	Proton Nuclear Magnetic Resonance Spectroscopy
d	Doublet
dd	Doublet of doublet
DPPH	Diphenylpicrylhdrazyl
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
ºC	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
s	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	Trimethyllsilyl propionic acid –d4 sodium salt
HMBC	Heteronuclear Multiple-Bond Correlation
CMC	Carboxymethyl cellulose

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}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}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 loses. 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 ^{1}H-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}H-NMR-based metabolomics.

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