# *ERGOGENIC EFFECT OF MENGKUDU (Morinda citrifolia L.) LEAF EXTRACT ON OBESE SPRAGUE DAWLEY RATS USING METABOLOMIC APPROACH*

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**FSTM 2019 26**

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By

**NORDIANA BINTI ABDUL MAJID**

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

**April 2019**

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Master of Science

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**April 2019**

**Chair : Professor Azizah Abdul Hamid, PhD**
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Natural products are getting much acceptance as ergogenic aids, in enhancing physical performance, not only among the athletes but also the general population. Obese person mostly has reduced desire and ability to exercise; resulting in difficulty to reduce weight and fat in the body. Thus, they need to boost their energy production so that they can be more active and healthier. In this study, *Morinda citrifolia* leaf extract (MLE) believed to possess ergogenic property was used to evaluate its effect on an obese animal model by using Forced Swimming Test (FST) as endurance exercise and the changes in metabolic profiles of exercise obese rats after treatment was also identified using $^{1}$H-NMR based metabolomics. The rats were fed with high fat diet (HFD) for 12 weeks for obese development. Once become obese, all the rats undergone endurance exercise every two weeks for 8 weeks together with treatment. Three different dosages of MLE used were 50 mg/kg, 100 mg/kg and 200 mg/kg of body weight (BW) together with two positive Control, 5 mg/kg caffeine and 100 mg/kg green tea. Blood and urine were collected for the metabolomic study. Animal study carried out showed that rats fed 200 mg/kg BW MLE demonstrated the longest endurance capacity of approximately three times as long as that of green tea and caffeine. The rats were also found to have lower lactate level, suggesting that energy metabolism was more effective in these rats. In addition, lactate dehydrogenase enzyme (LDH) activity, muscle injury indicator, was found to be lowest in rats fed the highest MLE level. Interestingly, the same effect was not seen in rats fed either caffeine or green tea, indicating that MLE treatment able to protect rat's muscle. In metabolomic, multivariate analysis including unsupervised and supervised analysis were used to identify the potential

biomarkers. The study showed that feeding the rats at a dose of 200 mg/kg BW MLE altered metabolites present in the serum of exercised obese rat. The PLS-DA score plots showed distinct separation between normal rats with that of green tea and caffeine treatments, and instead, were very similar to that of 200 mg/kg BW MLE suggesting that the 200 MLE feeding was more effective in improving endurance capacity in comparison to that of either synthetic or natural ergogenic substances. Metabolites such as glutamine, glycerol, glycine, acetoacetate, taurine, carnitine, succinate, pyruvate and 2-hydroxybutyrate were found to be higher after MLE treatment suggested that changes in metabolic pathways which included carbohydrate, lipid and energy metabolism. In conclusion, this study reports on the potential ergogenic property of high dose of MLE based on the enhancement swimming capacity, energy metabolism and metabolic perturbation in the exercised obese rats.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk Ijazah Master Sains

**KESAN ERGOGENIK DAUN MENGKUDU (*Morinda citrifolia* L.) TERHADAP TIKUS SPRAGUE DAWLEY OBESE MENGGUNAKAN PENDEKATAN METABOLOMIK**

Oleh

**NORDIANA BINTI ABDUL MAJID**

**April 2019**

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Produk semulajadi semakin diterima sebagai alat bantuan ergogenik, dalam meningkatkan prestasi fizikal, bukan sahaja di kalangan atlet tetapi juga di kalangan umum. Orang gemuk kebiasaannya telah berkurang keinginan dan keupayaan untuk bersenam; menyebabkan kesukaran untuk mengurangkan berat badan dan lemak di dalam badan. Oleh itu, mereka perlu meningkatkan pengeluaran tenaga supaya mereka boleh menjadi lebih aktif dan lebih sihat. Dalam kajian ini, ekstrak daun *Morinda citrifolia* (MLE) dipercayai mempunyai sifat ergogenik digunakan untuk menilai kesannya ke atas model haiwan obes dengan menggunakan Ujian Berenang Paksa (FST) sebagai latihan ketahanan dan perubahan dalam profil metabolik tikus gemuk yg berlatih selepas rawatan juga dikenalpasti menggunakan metabolomik berasaskan $^{1}$H-NMR. Tikus diberi makan dengan diet lemak tinggi (HFD) selama 12 minggu untuk menjadikannya obes. Setelah obes, semua tikus menjalani latihan ketahanan setiap dua minggu selama 8 minggu bersama-sama dengan rawatan. Tiga dos MLE berbeza yang digunakan ialah 50 mg / kg, 100 mg / kg dan 200 mg / kg berat badan (BW) bersama-sama dengan dua Kawalan positif, 5 mg / kg kafein dan 100 mg / kg teh hijau. Darah dan air kencing dikumpulkan untuk kajian metabolomik. Kajian haiwan menunjukkan bahawa tikus yang diberi makan 200 mg / kg BW MLE menunjukkan kapasiti ketahanan paling lama kira-kira tiga kali selagi teh hijau dan kafein. Tikus juga didapati mempunyai tahap laktat yang rendah, menunjukkan bahawa metabolisme tenaga lebih berkesan dalam tikus ini. Di samping itu, aktiviti enzim laktat dehidrogenase (LDH), penunjuk kecederaan otot, didapati paling rendah dalam tikus yang diberi peringkat tertinggi MLE. Menariknya, kesan yang sama tidak dilihat pada tikus yang diberi minum kafein atau teh hijau, menunjukkan bahawa rawatan MLE dapat melindungi otot tikus. Dalam analisis metabolomik, multivariate termasuk analisis yang tidak diselia dan diselia digunakan untuk mengenal pasti biomarker berpotensi. Kajian menunjukkan bahawa pada dos 200 mg / kg BW MLE mengubah metabolit yang hadir dalam serum tikus gemuk. Skop

skor PLS-DA menunjukkan pemisahan berbeza antara tikus normal dengan teh hijau dan rawatan kafein, dan sebaliknya, sangat mirip dengan 200 mg / kg BW MLE yang menunjukkan bahawa memberi makan dengan 200 MLE lebih berkesan dalam meningkatkan kapasiti ketahanan berbanding dengan bahan ergogenik sintetik atau semula jadi. Metabolit seperti glutamin, gliserol, glisin, acetonacetate, taurine, carnitine, succinate, piruvat dan 2-hydroxybutyrate didapati lebih tinggi selepas rawatan MLE menunjukkan perubahan dalam metabolisme karbohidrat, lipid dan tenaga. Sebagai kesimpulan, kajian ini melaporkan tentang potensi dos tertinggi MLE sebagai egen ergogenik berdasarkan keupayaan meningkatkan kapasiti berenang, metabolisme tenaga dan perubahan metabolik dalam tikus obes yang dijalankan.

**ACKNOWLEDGEMENTS**

Alhamdulillah, praised to Allah The Almighty, without His will no one can achieve anything such as my works today. I feel great gratitude for His graciousness and mercifulness in giving me strength and spirit everyday until I finished this research, and salawat to His messenger the beloved propet, Muhammad s.a.w who bring inspiration in my everyday life.

I would like to express my deep appreciation and gratitude to my supervisor committee chairman, Prof. Dr Azizah Abdul Hamid for her incalculable suggestion, guidance, patience, opportunity and support along my master's journey. I would like to express my gratitude to my other supervisory committee, Prof Dr Nazamid Saari and Assoc Prof Dr. Faridah Abas for their constructive comment, ideas and enthusiastic encouragement for this research work. My sincere gratitude also goes to SGS UPM for their financial support in term of scholarship provided to me during my postgraduate study period.

I would like to extend my thankfulness to all my friends particularly my lab mates that had contributed to my works by sharing ideas, giving comments and supports. Assistance provided by Universiti Putra Malaysia (UPM), Institut Biosains staff was greatly appreciated.

Finally, I would like to thanks to my parents, siblings and my husband for their incalculable support and strength in this journey of pursuing knowledge.

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

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| | |
|---|---|
| $^1$H NMR | Proton Nuclear Magnetic Resonance Spectroscopy |
| *D* | Doublet |
| *Dd* | Doublet of doublet |
| DPPH | Diphenylpicrylhdrazyl |
| g | Gram |
| HFD | High fat diet |
| HPLC | High Pressure Liquid Chromatography |
| LCMS | Liquid Chromatography Mass Spectrometry |
| *M* | Multiplet |
| MHz | Mega Hertz |
| mL | Milliliter |
| MLE | *M. citrifolia* leaf extract |
| Mmol | Millimole |
| ND | Normal diet |
| ºC | Degree in Celsius |
| OPLS-DA | Orthogonal Partial Least Squares–Discriminant Analysis |
| PC | Principal Component |
| PCA | Principal Component Analysis |
| PLS-DA | Partial Least Squares–Discriminant Analysis |
| *S* | Singlet |
| SIMCA | Soft Independent Modelling of Class Analogy |
| TPC | Total Phenolic Contents |
| VIP | variable importance in the projection |
| Δ | Chemical Shift in ppm |

# CHAPTER 1

## INTRODUCTION

Obesity is one of the most problematic condition worldwide, showing an increment in the risk of morbidity and mortality throughout most countries around the world. Malaysia known as Asian's fattest country, recorded an increase in its obesity rate, with the latest data showing half of its population are obese and overweight (NHMS, 2015). Obesity is related to metabolic perturbation that causes complications which include hypertension, hyperlipidaemia, diabetes mellitus, cancer and cardiovascular diseases. Exercise and reduction of caloric intake are most effective in making obese people to be healthier and have an active lifestyle (Mukherjee, 2003). Despite being the most effective way in weight management, individual's compliance is inconsistent, resulting from low performance and oxidative stress associated fatigue, justifying the need for better alternatives, including herbal sources. This is useful, in particular, for the herbs that possess ergogenic property.

Ergogenic aid is defined as substance that enhances the use of energy such as energy generation, efficiency and control. Athletes consume ergogenic aids to enhance their performances, elevate possibility to win in competitions, and improve their physicals (Silver, 2001; Palou and Bonet, 2007). Ergogenic aids will be beneficial for the obese and non-obese in efficient energy production and potentially in weight management as well as to improve health, have more active lifestyle and free from chronic diseases. There are many types of ergogenic aids such as doping agents (Saugy et al., 2006), amino acid and protein supplements (Kerksick et al., 2006), ginseng (Oliynyk and Oh 2013), caffeine (Beck et al., 2006) and some minerals (Williams, 2005). Creatine supplementation is an example of amino acid supplement that can be obtained naturally from meat. Creatine can act as dietary antioxidant because it can regulate oxidative stress (Sung et al., 2016). Caffeine is also regarded as ergogenic aid because it can enhance endurance by stimulating central nervous system. Some of ergogenic substances such as doping agents (anabolic steroids, growth hormone and other anabolic agents) are illegal and over consumption can lead to serious adverse effects including metabolic diseases, mental problem, cancer, renal and hepatic damage (Bird et al., 2016; Maravelias et al., 2005). Choosing the natural ergogenic aids are becoming more popular and might be a safer way to enhance performance without worrying any dangerous adverse effects. Nowadays, various plants and herbs have been shown to exhibit ergogenic property and this include Astragali radix (Li et al., 2014), capsicum (Lim et al., 1997) and ginseng (Bahrke and Morgan, 2000). Flavonoids content in some of the plants may contribute to the ergogenic property due to their potent antioxidant activity. Hence, study on ergogenic property of some plants are recommended because most plants and herbs possess antioxidant activity.

*Morinda citrifolia* commonly called 'mengkudu' in Malaysia was discovered more than 2000 years ago (Gerlach, 1996). There are various bioactive compounds that have been found in this plant including anthraquinones, anthraquinones glycosides, lignans, flavonol glycosides, phenlylpropanoids, saccharides, triterpenoids and fatty acids (Pawlus and Kinghorn, 2007). Each part of the plant (leaf, bark, stem, fruit and root) has different chemical composition and thus exhibits different biological activity. A study on bioactivities of *M. citrifolia* (Jambocus et al., 2016) revealed that the leaves extracted with 60 – 40% ethanol consisted more bioactive compounds and showed potent antioxidant activity as compared to that using 100% of ethanol. In the same study, the researchers reported the ability of *M. citrifolia* leaves extract in the prevention and treatment of obesity in the obese rats. In other study, *M. citrifolia* leaves water extract has been reported to enhance performance in swimming mice better than *M. citrifolia* fruit extract and green tea extract (Shalan et al., 2016). Despite as anti-obese and exhibit ergogenic property, this plant also has been studied for cancer treatment (Hirazumi et al, 1994), inflammation, diabetes, asthma, hypertension and pain (Solomon, 1999). There are many studies done on *M. citrifolia* activities, but the mechanisms of this plant as ergogenic property in an obese has not been discovered yet. Based on its potent antioxidant activity and ability to repair free radical damages and slow down oxidation process that might lead to oxidative fatigue, *M. citrifolia* leaf is expected to have ergogenic property.

Combination of exercise and consumption of the extract can cause changes in body metabolism that can increase energy production. Nuclear Magnetic Resonance (NMR) is one of the methods for metabolite assessment that involves in measuring the overall metabolic signature of biological samples. Metabolomics is most common available technology in detection, identification, quantification and differentiation of dynamic multivariate metabolic changes of biology system. Urine and blood serum are most widely used biofluid in metabolomics. Alteration in metabolomic profile also can be detected using urinary and serum metabolomics. Non-targeted approach of metabolomic using urine sample could provide new information related to development of food metabolome. Recent study by Hodgson et al., (2013) had identified the effects of drinking a green tea extract on the metabolic profiling of athletes by using $^{1}$NMR-based metabolomic. Results showed an effect of the green tea-based sports drink that is related with energy metabolism of athletes based on the metabolites identified. Hence, this approach will be used to investigate metabolic changes due to physical exercise in an obese rat.

**Problem Statements and Significant of the Study**

An obese person usually will easily suffer from fatigue upon physical exercises. This is the main problem faced by the obese individuals, when they want to do reduce their weight. Consequently, they are in need of substance that can boost their energy production so that they can be more active and have heathier lifestyle. Pharmaceuticals may help increase energy production but most of them will show many side effects. Hence, the use of a natural product that has ergogenic property with minimal side effect is recommended.

*M. citrifolia* leaf consisted of abundant of bioactive compounds that give benefits to human health. Previous studies, this plant leaf known to have potential as an anti-obesity property through *in vitro* and *in vivo* studies and its mechanism by using $^{1}$H-NMR approaches. However, there are no reported study on the ergogenic property of the same in high fat induced obese rats. By virtue of its antioxidant activity, this plant is expected to have an ergogenic property. Metabolomics is useful in confirming the effectiveness of the extract by identifying the changes of the metabolites produced by the different groups. Hence, this study hypothesizes that, the leaf extract of *M. citrifolia* exhibit the ergogenic property based on the perturbation of metabolic pathways in exercise high fat diet induced obese rat model.

The present study has been initiated with following objectives:

1) To demonstrate the ergogenic effect of *M. citrifolia* leaf extract in the obese rats using Forced Swimming Test.

2) To evaluate the effect of exercise on metabolic profile of obese rats using $^{1}$H-NMR based metabolomic.

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