UNIVERSITI PUTRA MALAYSIA

MECHANISM OF ANTI-OBESITY EFFECT OF OIL PALM (Elaeis guineensis Jacq.) LEAF METHANOLIC EXTRACT IN HIGH-FAT DIET-INDUCED OBESE MICE

TARLAN JAAFARPOUR

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By

TARLAN JAAFARPOUR

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

March 2019

DEDICATION

This thesis dedicated to

My Beloved Parents, Brother, Sister
Lecturers and Friends
Without Whom, None of My Success Would Be Possible
With Love, Tarlan

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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March 2019

Chairman : Professor Goh Yong Meng, PhD
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Obesity is a complex, multi-factorial, chronic disorder that can lead to the occurrence of a range of diseases, some of them life-threatening. Polyphenols like catechins received the most attention due to their reported anti-obesity properties. The methanolic oil palm leaf extract (OPLE) holds promise as a novel source of catechins due to its economic viability among other reasons. The aim of this study was to evaluate the possibilities of using OPLE as a rich source of catechins to mitigate obesity induced by feeding high-fat diets to mice.

Following 28 days subacute toxicity trial, histopathology of the lesions in both liver and kidney tissues revealed that administration of OPLE at 2000 mg/kg body weight, but not at dosage below 2000 mg/kg, induced noticeable tissue changes in both sexes such as necrosis and hydropic degeneration. This dosage is about 15 times higher than the working dose used in the current study.

In order to determine the effects of OPLE on high fat diet-induced obese mice, 4-week-old male ICR mice were assigned at random into six treatment groups of 10 mice each. Mice in the five high fat diet (HFD) groups were fattened using high fat diet from the onset of the experiment, while low fat diet (LFD) mice received normal diet throughout the 24-week trial. The OPLE and Orlistat treatments were given to the respective treatment groups once daily for between weeks 20 to 24 during the experimental period. Results showed that OPLE reduced the final body weight, organs weight and serum triglyceride (TG), total cholesterol (TC) concentrations, low-density lipoprotein cholesterol (LDL-C), ALT, AST, nitric oxide (NO), and the malondialdehyde (MDA) levels in muscle, but increased the serum high-density lipoprotein cholesterol (HDL-C). OPLE treatment in mice fed HFD resulted in

improved antioxidant status as evidenced by the increased superoxide dismutase (SOD), catalase (CAT), glutathione reductase (GR), glutathione peroxidase (GSH-Px), glutathione S-transferase and total anti-oxidant capacity (TAOC) levels of the serum. The OPLE treatment also increased the proportion of unsaturated fatty acids in the liver. The proportion of these beneficial fatty acids in muscles also increased in tandem with increasing OPLE dosages. Results also showed that the OPLE up-regulated the mRNA expression of PPAR-α, but down-regulated the mRNA expression of PPAR-γ, SREBP-1c, HSL and SCD-1 in the liver. These results suggested that OPLE could inhibit obesity partly by modulating the expression levels of genes involved in lipid oxidation and adipogenesis. OPLE also demonstrated a positive impact on obesity-induced inflammation by lowering TNF-α and IL-6 levels in the serum and regulating the levels of leptin and adiponectin concentrations in treated animals. Histological examination indicated that the size of the adipocytes was considerably reduced in animals treated with any of the three OPLE dosages in comparison to the HFD group. More importantly, OPLE treatment mice did not result in any adverse changes in the liver histology. In conclusion, these findings proof that OPLE treatments inhibited high fat diet-induced obesity in the mice model without any toxic adverse effects. Thus, OPLE holds promise as a potential nutraceutical or agent for the prevention and treatment for consideration against obesity in human populations.

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

MEKANISME ANTI-KEOBESAN EKSTRAK METHANOL DEDAUN KELAPA SAWIT (*Elaies guineensis* Jacq.) PADA MODEL MENCIT OBES

Oleh

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Keobesan merupakan keabnormalan yang kompleks, kronik dan diakibatkan oleh pelbagai faktor yang membawa kepada penyakit yang berbahaya. Polifenol, seperti katekin, menjadi tumpuan kajian kerana kesan anti-keobesannya. Ekstrak methanol dedaun kelapa sawit (OPLE) merupakan sumber katekin baharu yang mempunyai potensi ekonomi. Tujuan kajian ini adalah untuk menilai keberkesanan OPLE, sebagai sumber katekin untuk merawat keobesan yang disebabkan oleh diet lemak tinggi pada model mencit.

Kajian histopatologi pada tisu hati dan ginjal menunjukkan bahawa OPLE yang diberi pada dos 2000 mg/kg berat badan, menyebabkan perubahan nekrosis dan hidropik yang jelas kedua-dua jantina mencit selepas menjalani ujian ketoksikan subakut selama 28 hari. Dos ini adalah hampir 15 kali ganda dos maksimum yang digunakan dalam penyelidikan ini.

Kajian seterusnya beralih kepada penentuan kesan OPLE ke atas mencit obes yang diaruhkan oleh diet tinggi lemak. Dalam kajian ini, mencit jantan ICR berusia empat minggu dibahagikan secara rambang kepada enam kumpulan rawatan yang terdiri daripada 10 mencit pada tiap kumpulan. Mencit pada lima kumpulan diet lemak tinggi (HFD), digemukkan menggunakan diet lemak tinggi sejak dari awal eksperimen, sementara mencit dari kumpulan diet lemak rendah (LFD) menerima diet biasa sepanjang eksperimen 24 minggu tersebut. Rawatan OPLE dan Orlistat diberikan kepada kumpulan yang dikenalpasti secara harian daripada minggu 20 ke minggu 24 dalam tempoh eksperimen. Keputusan menunjukkan bahawa OPLE mengurangkan berat badan akhir, berat organ, tahap trigliserida dan jumlah kolesterol serum, LDL-C, ALT, AST, oksida nitrik (NO), dan tahap malonaldehid pada otot, dengan peningkatan HDL-C serum yang ketara. Rawatan dengan OPLE

pada mencit yang obes memperbaiki status antioksidaan tisu, seperti yang ditunjukkan oleh tahap superoksida dismutase (SOD), katalase (CAT), reduktase glutation (GR), peroksidase glutation (GSH-Px), S-transferase glutation dan kapasiti antioksidaan serum (TAOC). Rawatan OPLE juga meningkatkan perkadaran asid lemak tak tepu pada hati. Kandungan asid tak tepu juga meningkat pada tisu otot, seiring dengan peningkatan dos rawatan OPLE. Rawatan OPLE juga meningkatkan tahap ekspresi mRNA PPAR-α, tetapi mengurangkan tahap ekspresi PPAR-γ, SREBP-1c, HSL dan SCD-1 pada hati. Keputusan ini menunjukkan bahawa OPLE boleh merencat proses keobesan melalui kesannya ke atas gen yang mengawalatur oksidasi lipid dan adipogenesis. OPLE juga menunjukkan kesan positifnya dalam mengurangkan kecenderungan keradangan dengan mengurangkan tahap TNF-α, IL-6, leptin dan adiponektin pada serum. Cerapan histologi juga menunjukkan bahawa kumpulan mencit yang dirawat dengan OPLE menunjukkan saiz adiposit yang lebih kecil berbanding kumpulan obes kawalan HFD. Penemuan juga menunjukkan bahawa rawatan dengan OPLE tidak menunjukkan kesan ketoksikan pada hati mencit.

Kesimpulannya, OPLE telah menunjukkan potensinya dalam merencat keobesan pada model mencit tanpa sebarang kesan sampingan yang ketara. Sehubungan itu, OPLE memang terbukti mempunyai potensi kegunaan sebagai nutraseutikal, atau agen rawatan yang boleh dipertimbangkan untuk mengawal keobesan pada populasi manusia

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

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I hereby confirm that:

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LIST OF ABBREVIATIONS

ALT	Alanine transaminase
AST	Aspartate transaminase
BMI	Body mass index
BW	Body weight
CAT	Catalase
CVD	Cardiovascular disease
DM	Diabetes Mellitus
EGCG	Epigallocatechin gallate
FA	Fatty Acid
GR	Glutathione Reductase
GSH-Px	Glutathion peroxidase
GST	Glutathione S transferase
HDL	High density lipoprotein
HFD	High fat diet
HSL	Hormone Sensitive Lipase
HTN	Hypertension
IL-6	Interleukin-6
LDL	Low density lipoprotein
LFD	Low fat diet
MDA	Malondialdehyde
MUFA	Monounsaturated fatty acids / monoenoic fatty acids
NASH	Non-Alcoholic Steatohepatitis
NO	Nitric oxide

OPLE	Oil palm leaf methanolic extract
Pg/ml	Picogram /milli liter
PPARs	Peroxisome Proliferator-Activated Receptors
SOD	Superoxide dismutase
SREBP-1	Sterol Regulatory Element Binding Protein-1
TAOC	Total antioxidant capacity
TNF-α	Tumor necrosis factor alpha

CHAPTER 1

GENERAL INTRODUCTION

The accumulation of fats in both humans and animals is decided by the balance between dietary calorie intake and whole-body energy expenditure. If there is excess energy intake in comparison to energy expenditure, then excessive fat accumulation will occur, leading to the development of obesity (Bell et al., 2001; Hill et al., 2003). However, obesity could also occur due to complex genetic and/or environmental factors that promote the accretion of adipose. Obesity is an important risk factor for insulin resistance, type II diabetes, atherosclerosis, stroke, hypertension, impaired vascular function, sleep disorders, and cancer in human population (Nisoli & Carruba, 2004). Consequently, obesity or its treatment results in expensive health care expenditure that continued to escalate worldwide (Hill et al., 2003).

Over the past thirty years, obesity has become an increasing global health concern, which affects all age and ethnic groups. Based on the recent WHO report in 2016, more than 10% of the world's population is classified as obese in 2008, that is having a body mass index (BMI) of 30% or higher, and alarmingly, international obesity rates have increased by 100% since 1980 (WHO, 2016). In 2014, in excess of 1.9 billion adults, 18 years and older, were overweight and about a third of this population was obese. Among adults that were 18 years and older, 39% were overweight and a third were obese (WHO, 2016). Most countries are also experiencing worsening obesity crisis. In Malaysia, the Malaysian National Health and Morbidity Survey (2012) revealed that 33.3% of the adult population aged 18 and above (or 5.4 million) was pre-obese, while 27.2% (4.4 million) were obese. Among children younger than 18 years of age, 3.9% (or 0.3 million) were obese. Furthermore, the average Malaysian diet is not very healthy, because about 92.5% of adults aged 18 years and above ate less than five servings of fruits and vegetables daily. In Southeast Asia, the fattest country is Malaysia, while in the Asia-Pacific region the country is ranked sixth (Abdullah *et al*., 2015). Therefore, reducing the number of overweight people in Malaysia will help greatly in reducing the economic burden of obesity to the country's economy. However, reversing the obesity epidemic remained a challenge as anti-obesity drugs that are available are not very effective, and most have undesirable side effects (Nisoli & Carruba, 2004). Efforts are being made to reduce the rate of obesity among the population, but much more needs to be done because even a modest weight reduction of 5 to 7% in the obese person could reduce the risks of cardiovascular disease and diabetes significantly. Therefore, finding novel effective means for weight reduction is of utmost importance to human health (Nisoli & Carruba, 2004).

Globally, the strategy is to promote healthy dietary habits and make the necessary lifestyle adjustments. These ranged from managing caloric intake to practicing a more physically active routine to suppress obesity development (WHO, 2004). Much interest has also been devoted to research that investigated natural products with anti-obesity potential (Park & Kim, 2011; Rayalam *et al*., 2008). Such products are

normally those containing dietary phytochemicals that can potentially promote human health and prevent disease (Krzyzanowska *et al.*, 2010; Visioli *et al.*, 2006). These compounds have anti-obesity effects, which influenced a range of diverse metabolic pathways, such as absorption of lipids, intake and outflow of pre-adipocytes *et cetera* (Rayalam, Della-Fera, *et al.*, 2008). One of these candidate compounds that attracted a good degree of interest, and yet remained to be fully explores are the polyphenols, especially those from oil palm trees. Polyphenols are known to be phytochemicals with a diverse range of health benefits. A number of preclinical studies have found that polyphenols protect against a range of pathological conditions, especially those induced by oxidative stress such as CVD and metabolic disorders. Furthermore, dietary polyphenols could slow down the adipose tissue growth due to their anti-angiogenic activity, and by restricting metabolism in adipocytes (Badimon *et al*., 2010; Mulvihill & Huff, 2010).

Oil palm leaves is an under-used by-product of the oil palm industry, found in abundance in tropical South East Asia, Africa and South America (Jaffri *et al*., 2011). Oil palm leaf extract (OPLE) is not a conventional food ingredient but in recent times it has been found to give a range of health benefits. The OPLE contains higher levels of total polyphenols content compared to green tea, especially the glycosylated flavonoids, carotenoids and catechins (Irine *et al*., 2003). The health benefits of catechins in green tea have been known to prevent cancer, inflammation, arthritis, bacteria, angiogenesis, oxidative stress, virus, neuro-degeneration and hyper-cholesterolaemia (Khan & Mukhtar, 2007). However, the absence of reports on the anti-obesity effects of catechin-rich OPLE *in vivo* suggested that this compound remained an promising area for further research.

Research Problem:

The epidemic rise of obesity is not only a public health concern, but also resulted in significant economic burden to the nations at risk. Despite the increasing prevalence of obesity in human populations, the current treatment options remained ineffective and are complicated by hazardous side effects. Therefore, the current study investigated whether the methanolic extract from *Elaeis Guineensis* leaves is an effective anti-obesity agent using a high-fat diet induced obese mice model.

Justification of the study:

This study was justified, as obesity is already a global epidemic with serious health and economic consequences. Furthermore, the oil palm leaves used in the current study is a significant agricultural byproduct that remained underutilized, and has to be disposed off in a sustainable manner in tandem with the growth of the oil palm industry.

The present study hypothesised that:

1) Once daily oral administration of methanolic extract of *Elaeis Guineensis* leaves (OPLE) at 500, 1000 and 2000 mg/kg body weight doses will induce toxicity in male and female ICR mice
2) OPLE given at a daily dose of 50, 100 and 150 mg/kg will significantly reduce body weight gain that was caused by feeding high-fat diet.
3) OPLE will down-regulate important metabolic processes and biomarkers leading to a reduction in body weight in experimental mice subjects.

The objectives of the present study were:

1) To determine the subacute (28 days) toxicity studies of methanolic extract of *Elaeis guineensis* leaves (OPLE) in male and female ICR mice model.
2) To assess the impact of the OPLE on organs and body weights, serum biochemical parameters, markers of oxidative stress and antioxidant status of high fat diet-induced obese mice.
3) To determine the impact of OPLE on the mRNA expression profile of obesity-related genes, and changes in adipokine levels in high fat diet-induced obese mice.
4) To determine the histopathological changes in adipose cellularity and potential hepatoprotective effects of OPLE in the mice model.

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