EFFECT OF *Elateriospermum tapos Blume* IN AMELIORATING DEVELOPMENT PROGRAMMING OF MATERNAL OBESITY ON FEMALE OFFSPRING SPRAGUE DAWLEY RATS THROUGH MESOLIMBIC REWARD PATHWAY

By

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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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Early exposure to a high-fat diet increases the risk of obesity in later life. Recent animal studies have revealed that these offspring have a greater preference for fat, raising the possibility that prenatal exposure to high-fat foods alters the central reward system, increasing the desire to eat excessive amounts of palatable foods. *Elateriospermum tapos (E. tapos)* is a plant with a high phenolic and flavonoid content that has been shown to aid treatment of obesity in animal studies, which led to the hypothesise of *E. tapos* has the potential to prevent obesity among offspring as well. The present study has determined the effect of *E.tapos* in improving the developmental programming of maternal obesity on the female offspring's mesolimbic reward pathway. Throughout the study, the effect of *E. tapos* supplementation in obese rats before pregnancy on the female offspring's body weight, food intake, liver profile, kidney profile, lipid profile, stress hormone level, organ histology, cognitive effect, and the expression of mu-opioid receptor (MOR) as well as elements of the dopamine pathway; tyrosine hydroxylase (TH), dopamine receptor 2 (DR2) and the dopamine active transporter (DAT) were examined. A rat model of maternal obesity was generated using a high fat and cafeteria diet (HFCD) prior to and throughout pregnancy and lactation. Six rats out of 30 female Sprague-Dawley rats were assigned to the normal diet group. The remaining rats were fed with HFCD to generate obesity for 5 weeks. The obese rats were further divided into 4 groups of parent female (Dams); 1; Dams Negative Control (DNC, normal saline only), 2; Dams Positive Control (DPC, Orlistat drug 200mg/kg), 3; Dams Treatment 1 (DTX1, *E. tapos* seed 200mg/kg) and 4; Dams Treatment 2 (DTX2, *E. tapos* shell 200mg/kg) for 6 weeks daily before mating. The weaning offspring were then designated into 6 groups according to their dam's group (n = 6/group). Memory tasks for object and place recognition were conducted at 8th weeks of age. The offspring were culled at the 12th weeks of age for their organs and blood. The mesolimbic proteins were analyzed through the Western blot procedure. The

OTX2 group showed a decrease in weight gain, calorie intake, triglyceride, alanine aminotransferase, creatinine, Adrenocorticotropic and cortisol hormone level compared to ONC. Histological examination showed that liver and retroperitoneal white adipose tissue of OTX1 and OTX2 groups were comparable with the OND group. In memory tasks, OTX2 showed a significant increase in exploration rate in place test as compared to the ONC group. Finally, the MOR, TH, DR2 and DAT proteins in the mesolimbic region were found to be decreased in the ONC group and treatment with *E.tapos* had increased the proteins comparable with the normal diet group. Study showed that *E.tapos* seed and shell had ameliorated the changes in protein expression of dopamine and opioid pathways in offspring exposed to HFCD. Consequently, obesity-related parameters were normalized back to the normal level comparable to the normal diet group. This study highlights *E. tapos* seed and shell as an anti-obesity agent through the regulation of the mesolimbic pathway.

Keywords**:** *Elateriospermum tapos, high-fat diet, cafetaria diet, female offspring, mesolimbic pathway.*

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

KESAN *Elateriospermum tapos Blume* DALAM MEMPERBAIKI PENGATURCARAAN PEMBANGUNAN OBESITI IBU TERHADAP ANAK TIKUS BETINA SPRAGUE DAWLEY MELALUI LALUAN GANJARAN MESOLIMBIK

Oleh

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Pendedahan awal kepada diet tinggi lemak meningkatkan risiko obesiti di kemudian hari. Kajian haiwan baru-baru ini telah mendedahkan bahawa anak-anak tikus ini mempunyai kecenderungan terhadap makanan tinggi lemak, meningkatkan kemungkinan bahawa pendedahan pranatal kepada makanan tinggi lemak mengubah sistem ganjaran pusat, meningkatkan keinginan untuk makan secara berlebihan. *Elateriospermum tapos (E. tapos)* ialah tumbuhan dengan kandungan fenolik dan flavonoid yang tinggi yang telah terbukti dalam membantu rawatan obesiti tikus, mendorong kepada hipotesis bahawa *E. tapos* mempunyai potensi untuk mencegah obesiti dalam kalangan anak tikus juga. Kajian ini telah menentukan kesan *E.tapos* dalam meningkatkan pengaturcaraan perkembangan obesiti ibu ke atas laluan ganjaran mesolimbik anak tikus betina. Kajian memfokus kepada kesan suplemen *E. tapos* terhadap tikus yang obes sebelum hamil pada berat badan anak betina, pengambilan makanan, profil hati, profil buah pinggang, profil lipid, tahap hormon tekanan, histologi organ, kesan kognitif, dan ekspresi reseptor mu-opioid (MOR) serta unsur-unsur laluan dopamin; tyrosine hydroxylase (TH), reseptor dopamine 2 (DR2) dan pengangkut aktif dopamine (DAT). Model tikus obesiti ibu dihasilkan menggunakan diet tinggi lemak dan kafeteria (HFCD) sebelum dan sepanjang kehamilan dan penyusuan. Enam ekor tikus daripada 30 ekor tikus Sprague Dawley betina telah diberikan kepada kumpulan diet biasa. Tikus yang tinggal diberi makan dengan diet tinggi lemak dan kafeteria (HFCD) untuk menjana obesiti selama 5 minggu. Tikus-tikus obes itu dibahagikan lagi kepada 4 kumpulan mengikut kumpulan ibu tikus betina (*dams*); 1; *Dams* Kawalan Negatif (DNC, diet biasa), 2; *Dams* Kawalan Positif (DPC, Orlistat 200mg/kg), 3; *Dams* Rawatan 1 (DTX1, biji *E. tapos* 200mg/kg) dan 4; *Dams* Rawatan 2 (DTX2, cengkerang *E. tapos* 200mg/kg) ekstrak selama 6 minggu setiap hari sebelum mengawan. Anak-anak tikus betina setelah bercerai susu kemudiannya dibahagikan kepada 6 kumpulan mengikut kumpulan ibu mereka (n =

6/kumpulan). Tugas ingatan untuk pengecaman objek dan tempat telah dijalankan pada usia minggu ke-8 anak tikus betina. Anak-anak tikus betina dikorbankan pada usia 12 minggu untuk mendapatkan organ-organ dan darah. Protein mesolimbic dianalisis melalui prosedur Western blot. Kumpulan OTX2 menunjukkan penurunan dalam penambahan berat badan, pengambilan kalori, trigliserida, alanine aminotransferase, kreatinin, Adrenocorticotropic dan paras hormon kortisol berbanding ONC. Pemeriksaan histologi menunjukkan bahawa tisu adiposa putih hati dan retroperitoneal kumpulan OTX1 dan OTX2 adalah setanding dengan kumpulan OND. Dalam tugas ingatan, OTX2 menunjukkan peningkatan ketara dalam kadar penerokaan dalam ujian tempat berbanding kumpulan ONC. Akhirnya, protein MOR, TH, DR2 dan DAT di kawasan mesolimbic didapati berkurangan dalam kumpulan ONC dan rawatan dengan *E.tapos* telah meningkatkan protein yang setanding dengan kumpulan diet biasa. Hasil kajian menunjukkan bahawa benih dan cengkerang *E.tapos* telah memperbaiki perubahan dalam ekspresi protein laluan dopamin dan opioid dalam anak tikus betina yang terdedah kepada HFCD. Akibatnya, parameter berkaitan obesiti telah dinormalisasi kembali ke tahap normal setanding dengan kumpulan diet biasa. Kajian ini mengetengahkan biji dan cengkerang *E. tapos* sebagai agen anti-obesiti melalui pengawalan laluan mesolimbik.

Kata Kunci**:** *Elateriospermum tapos*, diet tinggi lemak, diet kafetaria, anak tikus betina, laluan mesolimbik.

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LIST OF ABBREVIATIONS

^{0}C	Degree celcius
ACE	angiotensin converting enzyme
ADHD	Attention-deficit hyperactivity disorder
ALA	alpha linolenic acid
AMPK	hypothalamic AMP-activated protein kinase
BMI	Body Mass Index
cm	Centimetre
CVD	Cardiovascular Diseases
D2R	dopamine 2 receptor
DAT	dopamine transporter
DNC	Dams Negative Control Group
DND	Dams Normal Diet Group
DPC	Dams Positive Control Group (200mg/kg Orlistat)
DTX1	Dams Treatment 1 (200 mg/kg *E.tapos* seed)
DTX2	Dams Treatment 2 (200 mg/kg *E.tapos* shell)
g	gram
HFD	High fat diet
kg/m^2	Kilogram per meter square
L	Liter
mg/kg	Milligram per kilogram
min	minutes
ml	Millileter
MORs/Mu	μ-opioid receptor
NAc	nucleus accumbens

NCD	non-communicable diseases
NHMS	National Health and Morbidity Survey
OCD	Offspring from normal diet but fed with cafeteria diet
ONC	Offspring from negative control dams
OND	Offspring from normal diet dams
OPC	Offspring from positive control dams
OTX1	Offspring from dams supplemented with 200 mg/kg *E.tapos* seed
OTX2	Offspring from dams supplemented with 200 mg/kg *E.tapos* shell
ppm	parts per million
ROS	Reactive oxygen species
RpWAT	retroperitoneal white adipose tissue
TH	thyrosine hydroxylase
TLR4	Toll-like receptor
VTA	Ventral Tegmental Area
WHO	World Health Organization

CHAPTER 1

INTRODUCTION

1.1 Research Background

Obesity is currently a crucial global medical problem as it is related to serious complications from non-communicable diseases (NCDs) such as cardiovascular diseases, type two diabetes and various types of cancers (Pell et al., 2016). The global obesity prevalence continues increasing unabatedly with 2.7 billion adults are predictable to be overweight or have obesity by 2025. An obesity rate differs particularly across South East Asia, with Malaysia recording amongst the highest levels. According to National Health and Morbidity Survey in 2019, prevalence of obesity In Malaysia among female is higher compared to male (54.7% in females; 45.3% in males).

Global Nutrition Report 2017 has shown that 54% of overweight or obese women are of childbearing age (Development Initiatives, 2017). Two main factors that may lead to overweight or obesity during childbearing age are excessive gestational weight gain and subtle changes in behaviour or lifestyle such as increased caloric intake, a less healthy diet and reduced physical activity in the ostpartum period. Maternal obesity is at higher risk of having a baby that is large for gestational age, and overweight or obese in childhood (Guelinckx et al., 2008). Obesity among children has becoming serious global issues as the prevalence was increasing every year (Abarca-Gómez et al., 2017). In 2016, without a doubt the number of obese children wherever all through the world were assessed to be 124 million. In 2019, NHMS reported 29.8% of children aged between 5 to 17 years are overweight or obese. High BMI in early ages regularly causes the development of chronic diseases in adulthood such as cardiovascular diseases and type II diabetes (Park et al., 2019).

All these insights above indicate why an extensive multilevel solution to childhood obesity needs to be put forward for future generations to achieve a healthier lifestyle. It is therefore essential to treat obesity as it is the cause of many illnesses. The prevalent side effects of standard obesity medicine such as headache, constipation, cardiac arrhythmia, and more illnesses have led to the increased use of traditional herbal medicine (Osada et al., 2003). Consequently, procedures using comparatively secure and less side effects of natural products are gaining interest in curing obesity.

In recent discovery, medicinal values in *Elateriospermum tapos* (*E. tapos*) plant have been suggested as an alternative treatment for combating maternal obesity which then will reduce risks of severe comorbidities in offspring. E.*tapos*

is a species of plant of Euphorbiaceace family and are classified into subfamily of Crotonoideae and Elateriospermeae tribe. Widely found in Southeast Asian tropical rainforest which includes peninsular Malaysia, peninsular Thailand, Brunei, Sumatra, Java and Borneo. *E.tapos* commonly applied in wound healing treatment (Corner, 1989), and treating chronic diseases such as hypertension (Yong and Salimon, 2006). The preliminary study on *E.tapos* seed and shell extracted with hot water extraction obtained the highest phenolic and flavonoid content and exhibited the best pancreatic lipase and antioxidant activity (Nor Liyana et al,. 2019). Observing the beneficial correlation between phenolic and flavonoid compounds and free radical scavenging and anti-lipase activity proposed that these compounds were accountable for *E.tapos* extraction's anti-obesity and anti-oxidant impact.

This research evaluated the potential of *E.tapos* seed and shell treatment prior pregnancy of obese rat to their first-generation specifically their female adult offspring at their 12th week of age. The body and organ weight, calorie intake, lipid profile, liver and kidney function test histological changes of the vital organ and also behavioural changes among the first generation of research rats were studied. Research also focusing in the investigation of protein expression like thyrosine hydroxylase (TH), dopamine 2 receptor (D2R), dopamine transporter (DAT) and μ-opioid receptor (Mu) control for food addiction in the mesolimbic reward pathway of offspring.

1.2 Problem Statement

Maternal nutritional parameters during pregnancy may have noticeable effects on foetal growth and ultimately influence the offspring's predisposition to obesity, as has been well established in human research and animal models. Studies looking at the developmental causes of adult obesity have shown that gestational diabetes, maternal obesity, and weight gain during pregnancy are all linked to an increased chance of the offspring developing obesity throughout childhood or as an adult. Recent research on humans has shown that of these variables, maternal pre-pregnancy weight may be the most indicative of offspring obesity (Desai et al, 2014). Animal studies have begun to examine the mechanisms of foetal programming, with evidence that maternal obesity and a Western high-fat (HF) diet programme foetal adipose tissue to promote increased adipogenesis and hypothalamic neural pathways to promote appetite as compared with satiety, but fail to overcome the "hedonic" aspect of feeding, the drive for reinforcing food stimuli.

Public awareness and knowledge on maternal obesity and its outcomes towards childhood obesity is yet low and it is often neglected. Therefore, there is a need to address suitable care and disease management of obese in pregnant women using alternatives such as natural remedies or traditional medicines. Worldwide, there are many research on the alternative medicine using natural herbs as an intervention of obesity. However, most of research focusing on reducing body

weight and others parameter related to obesity for one generation only. The mesolimbic reward system, which comprises dopamine and opioid-related genes, was found to be altered in the expression of offspring exposed to high fat and high sugar diets during pregnancy by Vucetic et al. in 2010. However, few studies have examined the precise molecular mechanism behind anti-obesity action (Karri et al.2019). This current study focused on the female offspring because female offspring will grow up and produce their own offspring, therefore we will be able to cut off the vicious cycle of obesity transgenerational effect. This new finding will aid to decrease the prevalence of children suffering from childhood obesity and any comorbidities.

1.3 Objective

1.3.1 General objective

This research aims to examine the beneficial effects of *E-tapos* supplementation prior pregnancy period in order to ameliorate the developmental programming of maternal obesity on female offspring mesolimbic reward pathway.

1.3.2 Specific objectives

1. To determine the effects of *E.tapos* supplementation in obese dams prior to pregnancy on the obesity development precursor through changes of body weight, food intake and histology study on retroperitoneal white adipose tissue (RpWAT) of female offspring.

2. To investigate the effects of *E.tapos* supplementation in obese dams prior to pregnancy on obesity related stress through evaluation of plasma corticosterone and adrenocorticotropic hormone level of the female offspring.

3. To evaluate the toxicity effects of *E.tapos* supplementation in obese dams prior to pregnancy through liver profile test, histology study of liver and kidney of the female offspring.

4. To investigate the effects of *E.tapos* supplementation in obese dams prior to pregnancy on the cardiovascular disease development through lipid profile analysis, atherosclerotic lesion development and heart histology analysis of the female offspring.

5. To evaluate the effects of *E.tapos* supplementation in obese dams prior to pregnancy on the cognitive function and behavioral of female offspring on their 8th weeks of age.

6. To determine the effects of *E.tapos* supplementation in obese dams prior to pregnancy in ameliorating the impact of the maternal obesity in female offspring, via examinations of female offspring mesolimbic reward pathway indicated by thyrosine hydroxylase (TH), dopamine 2 receptor (D2R), dopamine transporter (DAT) and μ-opioid receptor (Mu) protein expression.

7. To correlate the food intake and bodyweight of the female offspring with the parameters measured in the plasma and brain tissue.

1.3.3 Hypothesis

Maternal obesity leads to permanent changes within the mesolimbic reward pathway in the offspring of obese dams, which altered the protein expression of Thyrosine hydroxylase (TH), Dopamine 2 receptor (D2R), Dopamine transporter (DAT) and μ-opioid receptor (Mu). This impact on the female offspring can be ameliorated via supplementation of *E.tapos* in obese dams prior to pregnancy.

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