



UNIVERSITI PUTRA MALAYSIA

***POTENTIAL OF Elateriospermum tapos Blume IN AMELIORATING
MATERNAL METABOLIC SYNDROME ON FEMALE OFFSPRING OF
SPRAGUE DAWLEY RATS THROUGH THE HYPOTHALAMIC FEEDING
CIRCUITRY***

SANTHRA SEGARAN A/L BALAN

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By

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**Thesis Submitted to the School of Graduate Studies,
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September 2022

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Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfillment of the requirement for the degree of Doctor of Philosophy

POTENTIAL OF *Elateriospermum tapos* Blume IN AMELIORATING MATERNAL METABOLIC SYNDROME ON FEMALE OFFSPRING OF SPRAGUE DAWLEY RATS THROUGH THE HYPOTHALAMIC FEEDING CIRCUITRY

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Maternal obesity is often related to balancing daily lifestyle intake of high-fat diet or western diet. This will affect endogenously on altering the daily activity of metabolism and lead to childhood obesity. The central nervous system (CNS) plays a vital role in regulating food intake and energy usage to maintain the energy balance in the body. Specifically, the hypothalamus monitors and response to the peripheral signal such as Neuropeptide Y (NPY), proopiomelanocortin (POMC) and leptin receptor (Obr), which involve feeding circuitry organisms. *Elateriospermum tapos* (*E.tapos*) known as buah perah locally and contain flavonoid in seed and shell which help reduce body weight. This study investigates the effect of *E. tapos* supplementation on female offspring through hypothalamic feeding circuitry. Thirty adult female Sprague Dawley rats were divided into two groups. Six rats assigned as a control group (DCG) were fed with standard chow, and 24 rats were assigned to an obese group with a high-fat diet (HFD) and cafeteria food to generate obesity for five weeks. HFD rats were later assigned as negative group (DNG), positive group (DPG) with 200mg/kg of orlistat drug, treatment 1 (DTX1) with 200 mg/kg *E.tapos* seed, and treatment 2 (DTX2) with 200 mg/kg *E.tapos* shell daily for six weeks. Female rats were mated and culled at postnatal day 21 (PND21). Organs, blood, and brain were collected for analysis. Dams from the DTX2 group slightly reduced body weight and retroperitoneal whited adipose tissue (RpWAT) compared to the DNG group. Their offspring from treatment 2 (OTX2) offspring; show the same effect at mother dams. Total cholesterol levels among DTX2 and OTX2 show a significant decrease ($p<0.05$) in dams and offspring. The atherosclerotic lesion was present in group DTX1, DTX2, offspring from treatment 1 (OTX1), and OTX2 compared to DNG and offspring from negative (ONG) group rats. Liver profile on alanine transaminase and aspartate transaminase level show significant changes ($p<0.05$) among all dams and offspring. Histopathological grading of the liver section of DNG, ONG, and

offspring from positive (OPG) displayed the presence of ballooning hepatocytes. Histology of RpWAT of DTX1, DTX2, OTX1, and OTX2 showed normal adipocytes with a similar pattern of DCG and offspring from the control (OCG) group. Plasma leptin shows significant changes ($p < 0.05$) among DTX2 and OTX2 compared to DNG and ONG groups. Expression of protein OBR, POMC, and NPY was analyzed using a western blot. Results show that the expression in DNG and ONG from this protein is more prominent than in other groups. In conclusion, the *E.tapos* shell had a more significant effect on ameliorating maternal obesity on female offspring at PND21 than the *E.tapos* seed.

Keywords: *Elateriospermum tapos*, maternal obesity, lipid profiles, toxicity



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

**KAJIAN MENGENAI POTENSI *Elateriospermum tapos* Blume DALAM
MEMPERBAIKI METABOLIK SINDROM PADA ANAK TIKUS BETINA
SPRAGUE DAWLEY MELALUI KAWALAN PEMAKANAN DI
HIPOTALAMUS**

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Obesiti ibu sering dikaitkan dengan tiada keseimbangan gaya hidup harian dari segi pengambilan diet tinggi lemak atau pengamalan makanan gaya hidup barat. Ini akan memberi kesan secara endogen ke atas perubahan aktiviti harian metabolisme dan membawa kepada obesiti dikalangan kanak-kanak. Sistem saraf pusat (CNS) memainkan peranan penting dalam pengawalan pengambilan makanan dan penggunaan tenaga untuk mengekalkan keseimbangan tenaga dalam badan. Khususnya hipotalamus adalah pusat pemantauan dan tindak balas dengan memberi isyarat periferi seperti protein NPY, OBR dan POMC yang terlibat dalam kitar pemakanan. Kajian ini bertujuan untuk mengkaji kesan suplemen *Elateriospermum tapos* terhadap tikus betina melalui kawalan pengambilan makanan di hipotalamus. Tiga puluh ekor tikus Sprague Dawley betina dewasa dibahagikan kepada dua kumpulan. Enam tikus yang diketogorikan sebagai kumpulan kawalan (DCG) diberi makan yang biasa dan 24 ekor tikus diketogorikan kepada kumpulan obes dengan memberikan diet tinggi lemak (HFD) dan makanan kafeteria untuk menjana obesiti selama 5 minggu. Tikus HFD kemudiannya dibahagikan kepada kumpulan negatif (DNG), kumpulan positif (DPG) dengan 200mg/kg ubat orlistat, rawatan 1 (DTX1) dengan 200 mg/kg biji *E.tapos* dan rawatan 2 (DTX2) dengan 200 mg/kg kulit *E.tapos* setiap hari selama 6 minggu. Tikus betina mengawan dengan tikus jantan dan dibunuh pada hari ke 21 selepas bersalin. Organ, darah dan otak dikumpul untuk dianalisis. Tikus betina daripada kumpulan DTX2 menunjukkan sedikit pengurangan berat badan dan tisu adipos putih retroperitoneal (RpWAT) berbanding kumpulan DNG. Pengurangan berat badan juga diperhatikan pada anak-anak mereka daripada kumpulan rawatan 2 (OTX2) anak, ia menunjukkan kesan yang sama seperti tikus ibu. Jumlah tahap kolesterol di kalangan DTX2 dan OTX2 menunjukkan penurunan yang ketara ($p < 0.05$) dalam tikus betina dan juga dalam anak. Lesi aterosklerotik hadir dalam kumpulan DTX1, DTX2, OTX1 dan OTX2 berbanding tikus dari kumpulan DNG

dan ONG. Aras alanine transaminase dan aspartate transaminase (di hati) menunjukkan perubahan ketara ($p < 0.05$) di kalangan semua tikus betina dan anak tikus. Penggredan histopatologi bahagian hati DNG, ONG dan adalah normal berbanding daripada tikus kumpulan positif (OPG) menunjukkan kehadiran hepatosit belon. Histologi RpWAT DTX1, DTX2, OTX1 dan OTX2 menunjukkan adiposit yang normal sama seperti kumpulan DCG dan trend yang sama kelihatan kepada anak tikus. Plasma leptin menunjukkan perubahan ketara ($p < 0.05$) di kalangan DTX2 dan OTX2 berbanding kumpulan DNG dan ONG. Ekspresi protein OBR, POMC dan NPY dianalisis menggunakan Teknik western blot. Keputusan menunjukkan ekspresi dalam DNG dan ONG daripada protein ini lebih menonjol berbanding kumpulan lain. Kesimpulannya, kulit buah *E.tapos* mempunyai kesan yang lebih bagus dalam memulihkan obesiti ibu terhadap anak tikus betina pada PND21 berbanding dengan biji *E.tapos*.

Kata kunci: *Elateriospermum tapos*, obesiti ibu, profil lipid, ketoksikan

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LIST OF ABBREVIATIONS

AgRP	Agouti-related peptide
ALA	Alpha-linolenic acid
ALP	Alkaline phosphatase
ALT	Alanine transaminase
APS	10% ammonium persulfate
ARC	Arcuate nucleus
AST	Aspartate transaminase
ATP	Adenosine triphosphate
BAT	Brown adipose tissue
BMI	Body Mass Index
CART	Cocaine- and amphetamine-regulated transcript
CCK	Cholecystokinin
CF	cafeteria food
CKD	Chronic kidney disease
CNS	Central nervous system
DCG	Dams Control group
DMH	Dorsomedial Hypothalamus
DNG	Dams negative control group
DPG	Dams positive control group
DTX1	Dams treatment group 1
DTX2	Dams treatment group 2
<i>E.tapos</i>	<i>Elateriospermum tapos</i>
EPA	Eicosapentaenoic acid
GCs	Glucocorticoids

GH	Growth hormones
GR	Glucocorticoids receptor
H & E	Hematoxylin & Eosin
HDL	High density lipoprotein
HFD	High fat diet
IR	Insulin receptor
LDH	Low-density lipoprotein
LSD	Least significant difference
MC4R	Melanocortin-4-receptor
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
NBF	Natural buffer formalin
NHMS	National Health Morbidity Survey
NPY	Neuropeptide Y
ObR	Leptin Receptor
OCG	Offspring control group
ONG	Offspring negative control
OPG	Offspring positive group
OTX1	Offspring from dams treatment 1
OTX2	Offspring from dams treatment 2
PND 21	Postnatal day 21
POMC	Proopiomelanocortin
PPAR	Peroxisome proliferator activator receptor
PUFAs	Polyunsaturated unsaturated fats
PVN	Paraventricular nucleus

RpWAT	Retroperitoneal white adipose tissue
SREBP	Sterol regulatory element-binding protein
TC	Total cholesterol
TEMED	N, N, N', N'-Tetramethyl ethylenediamine
TG	Triacylglycerol
WAT	White adipose tissue
WHO	World Health Organization
α - MSH	α melanocyte stimulating hormone

CHAPTER 1

INTRODUCTION

1.1 Overview

Fat is beneficial in the body because it provides energy and acts as a cushion to prevent shock. Too much fat is unhealthy because it can lead to many medical severe diseases. Excessive body fat is a severe medical condition which is known as obesity. Different age groups have different Body Mass Index (BMI) scales, and the scale is even different between both genders. A few methods measure body fat through waist circumference, BMI, and skinfold thickness (Hamer & Stamatakis, 2012).

The World Health Organization indicates that an individual is considered overweight when BMI 25 to 29.9 kg/m² and obese when BMI achieves 30.0 kg/m². Additionally, can measure waist circumference that is related to stomach fat. The typical abdomen/waist circumference range for men is under 40 inches, while for ladies under 35 inches. The high health danger can be resolved with weight gain around the stomach region because the fat is more dynamic.

Obesity can influence metabolic profiles such as glucose metabolism, adverse lipid profiles, and increased blood pressure. Obesity is highly associated with diabetes type 2 and cardiovascular disease. Other medical complications include cancer, stroke, cataracts, pulmonary disease, and gall bladder disease. Besides, there are two main ways of obtaining obesity (Reilly et al., 2005). Firstly, through genetic factors followed by environmental factors. Thus, supplementation could be a potential cure for obesity caused by both factors.

The abundance of stomach fat causes the expansion in blood cholesterol prompts blood cluster and aggravation that can cause heart assaults and strokes. Asian tends to have a more noteworthy stomach fat at their lower BMI. This causes the danger of obesity that is identified with morbidity and mortality among Asian people. The perpetual irregularity and vitality consumption prompts overabundance of vitality stockpiling as fat (Jéquier, 2002). Other than that, the ascent of corpulence is credited to an individual free current way of life and familial factors, such as hereditary and condition (Caruso, Chen, and Morris, 2011). A person's hereditary qualities are more active in advancing weight, and moms dictate early life-nourishing. Weight is related to a few fatalities.

This includes breast tumor, malignancy of the liver, thyroid development, colon, ovarian tumor, and multiple myeloma. The omnipresence of heftiness has been a mental rise over the last few decades. In 2014, over 1.9 billion people over 18,600 years old were overweight, and 600 million were heavy (WHO, 2014). In

2014, 13% of the world's population was obese. The highest fat level is 15 percent for women than for men, 11 percent. In Southeast Asia, the most crucial area of stoutness is Malaysia, which is 14 percent, and Thailand is the second most notable country, which is 8.8% (Wu, 2006).

Maternal obesity refers to the condition of the pregnant mother being overweight. It is risky that women of reproductive age present this kind of disease. This impacts the mothers, but it also affects the offspring. Obesogenic is the type of transmission causing obesity to the offspring due to the inheritance passed by the maternal (Samuelsson et al., 2008). This trait that has obese characteristics can be passed from generation to generation. The prevalence of childhood obesity has increased, and this case has become an epidemic in recent years. In a nutshell, the potential risk factors of obesity should be identified to take preventive methods. Obesity does not only influence physically but also affects children socially and emotionally. They tend to have low self-esteem and are not confident enough in performing a particular task (Straus, 2000).

Obesity during pregnancy can alter the offspring's hypothalamic appetite gene expression associated with an increased preference for high fat and high sugar junk food (Mukesh R, et al. 2015). A preliminary study (in vitro) showed that *E. tapos* inhibits pancreatic lipase, α -glucosidase, and α -amylase enzymes. *E. tapos* contains oleic acid and α -linolenic acid (16.10%), omega-three polyunsaturated fatty acid (Yong Y, 2006). Another study conducted by researchers shows that *E. tapos* also help reduce obesity due to a high level of flavonoid n it help in fat oxidation (Perumal K.V et al., 2019).

1.2 Problem Statement

The prevalence of children being obese has gradually increased over these past years. According to the National Health Morbidity Survey (NHMS) (2019), the statistics show that more than 21.8% of children below five years old are categorized as overweight or obese, and it increased from 2011 prevalence (16.6%) and 17.7% from 2015. The prevalence of overweight children ranging from 7 to 12 years old was 15%, and obese were 14.8%. Obesity had become endemic to certain developed countries. Children are the country's future, and the determinants of the success of our country are at risk of exposure to this serious medical condition.

Obesity is not a contagious disease, yet it is obtained through unhealthy lifestyles, such as eating more and less physical activity (Williams, Mackenzie, & Gahagan, 2014). The public awareness of obesity and its risk factor is not high enough. Obesity is associated with many diseases, especially heart-related diseases, leading to mortality. Hence, intervention strategies should be discovered to prevent or minimize the prevalence of obesity. Studies in human and animal models have proven that obesity in women of reproductive age and during pregnancy may influence or program appetite, affect metabolic regulation,

and increase the risk of significant disease in their children, which will last long till adulthood.

Therefore, there is a need to address proper care and disease management of obese pregnant women using alternatives such as natural remedies or traditional medicines. Therefore, proper wellness management must be taken care of beside medication consumption. This includes having a healthy dietary intake, exercising, and consuming extra supplements. Not all supplementation is helpful for everyone. *E.tapos* has a high content in protein, which acts as a natural source in boosting metabolism. Through this supplementation, the prevalence of obesity can be significantly reduced. By conducting this research, we can identify the efficacy of *E.tapos* supplementation and may upgrade the experimental study by identifying the effect of *E.tapos*. It can also be used to shed some light on this matter to the public on the importance of supplementation.

1.3 Objective

1.3.1 General objective

This research aims to examine the beneficial effects of *E. tapos* supplementation prior to pregnancy to ameliorate the developmental programming of maternal obesity on female offspring's hypothalamic appetite protein expression.

1.3.2 Specific objective

1. To determine the effect of *E. tapos* supplementation in obese dams prior to pregnancy on dams body weight, food intake, plasma leptin, and hypothalamic protein expression of NPY, POMC, and ObR.
2. To correlate the effect of *E. tapos* supplementation in obese dams prior to pregnancy by comparing the impacts on maternal obesity in female offspring body weight.
3. To determine the effect of *E. tapos* supplementation in obese dams prior to pregnancy in alleviating the impact of the maternal obesity in female offspring via examination of lipid profiles, liver profile, creatinine level and leptin.
4. 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 offspring hypothalamic appetite control indicated by NPY, POMC, and ObR protein expression.
5. To determine the effects of *E. tapos* supplementation in obese dams prior to pregnancy on the morphology of the offspring liver, retroperitoneal white adipose tissue, kidney, and heart via Hematoxylin & Eosin (H&E) stain and erythematous plaque via Sudan IV stain.

1.3.3 Hypothesis

Maternal obesity alters the female offspring's hypothalamic appetite protein expression NPY, POMC, and ObR. This impact can be ameliorated via supplementation of *E. tapos* in obese dam's prior pregnancy.

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