EFFECTS OF CRUDE METHANOLIC LEAF EXTRACT OF Clinacanthus nutans (BURM.F.) LINDAU ON HIGH-FAT DIET-INDUCED OBESE MICE

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FPV 2020 14

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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

September 2019

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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September 2019

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Obesity is a major health concern that has reached epidemic proportions globally. Malaysia has the highest obesity rate at 14% in the Southeast Asia region. The cost and side effects of synthetic anti-obesity drugs necessitate the finding of suitable herbal alternatives. The current study investigated the antiobesity effects of *Clinacanthus nutanus* crude leaf extract in 80 % methanol (MECN). The sub-acute oral toxicity of MECN was evaluated in 6-week- old ICR mice (21 males, 21 females). The mice were randomly divided into six treatment groups of seven animals each, comprising of untreated control, mice treated with 1000 and 2000 mg/kg MECN, for males and females. Animals were gavaged with the treatment agents once daily for 28 days. Despite the incidental lesions noted for the livers and kidneys, there no difference ($P>0.05$) between the histolopathological changes seen among mice treated with MECN, and that of the untreated controls in both sexes. No significant changes were also noted for the physical, hematological and serum biochemical parameters between the control and treatment groups for both sexes. However, the serum sodium level in mice treated with 2000 mg/kg MECN was lower than the controls ($P<0.05$). In the ensuing experiment, MECN was used at 2000 mg/kg as a potential anti-obesity agent in obese mice. Fifty (4-weeks-old) male mice were randomly assigned into 2 groups: (1) a normal diet group (NC, n=10); and (2) treatment group (fed a high-fat diet for 16 weeks, n=40). At 20 weeks of age, the mice fed high-fat diet were randomly assigned into 4 sub-groups comprising of, high-fat diet only (HFDC); MECN at 500 mg/kg (HFD+CN500); 1000 mg/kg (HFD+CN1000) and 1500 mg/kg (HFD+CN1500). All mice were then subjected to 21 days of treatment. The current study showed that MECN treatment at 1000 and 1500 mg/kg reduced body weight, relative visceral fat, serum lipid profile, malondialdehyde (MDA) levels in muscle, cholesterol and saturated fatty acid composition ($P<0.05$). Visceral fat among MECN-treated mice showed significant decrease ($P<0.05$) in hypertrophic adipocyte cell size compared to the HFDC group after treatment. The PPARγ and SCD1 genes expression

were down-regulated, especially in mice fed with 1000 and 1500 mg/kg of MECN compared to the HFDC group. Mice treated with MECN at 1500 mg/kg showed a decreased PPARα expression, and an increased expression of HSL mRNA. In terms of adipocytokines, mice treated with MECN at 1000 and 1500 mg/kg showed a significantly ($P<0.05$) elevated level of adiponectin, and reduced levels ($P<0.05$) of leptin, interleukin-6 (IL-6), and tumor necrosis factor-α (TNFα) compared to the HFDC. In summary, the results suggested that MECN could ameliorate diet-induced obesity via the regulation of gene expressions and adipocytokines involved in lipid metabolism. However, future clinical trials are necessary to ascertain its clinical efficacy.

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

KESAN EKSTRAK MENTAH METANOL DAUN *Clinacanthus nutans (*BURM.F.) LINDAU KE ATAS MENCIT OBES YANG DIARUH OLEH DIET

Oleh

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Obesiti adalah masalah kesihatan utama di seluruh dunia. Malaysia mempunyai prevalens obesiti tertinggi di Asia Tenggara pada 14%. Kos dan kesan sampingan ubatan anti-obesiti sintetik mendesak keperluan untuk alternatif herba yang sesuai. Kajian ini menyelidik kesan ekstrak mentah daun *Clinacanthus nutanus* dalam 80 % metanol, (MECN) terhadap obesiti. Ketoksikan sub akut MECN dikaji pada mencit ICR berumur enam minggu (21 jantan dan 21 betina). Mencit dibahagikan secara rawak kepada enam kumpulan yang mengandungi tujuh individu setiap satu, yang terdiri daripada, kumpulan kawalan yang tidak dirawat, kumpulan mencit yang dirawat dengan MECN 1000 mg/kg; dan mencit dirawat dengan MECN 2000 mg/kg, untuk kedua-dua jantina. Dos rawatan diberikan secara gavaj setiap hari selama 28 hari. Walaupun terdapat lesi insidental pada hati dan ginjal, tiada perbezaan ($P>0.05$) perubahan histopatologi di antara mencit kawalan dengan mencit yang dirawat dengan MECN untuk kedua-dua jantina. Tiada perubahan juga dicerap pada parameter fizikal, hematologi dan biokimia pada kedua-dua jantina ($P>0.05$). Walaubagaimanapun, tahap natrium serum pada mencit yang dirawat dengan MECN pada 2000 mg/kg, adalah lebih rendah berbanding kawalan ($P<0.05$). Dalam eksperimen berikutnya, MECN digunakan pada 2000 mg/kg untuk merawat mencit yang telah diaruh menjadi obes menggunakan diet. Lima puluh ekor mencit jantan ICR berumur empat minggu dibahagikan ke dalam dua kumpulan secara rawak: kumpulan diet biasa (NC, n=10), dan kumpulan mencit yang diberi makan diet tinggi lemak (60% tenaga makanan dari lemak selama 16 minggu, n=40). Pada usia 20 minggu, mencit yang diberi makan diet lemak tinggi diasingkan kepada 4 sub-kumpulan secara rawak, yang terdiri daripada: mencit diet lemak tinggi (HFDC); mencit menerima rawatan MECN pada 500 mg/kg (HFD + CN500); mencit menerima MECN pada 1000 mg/kg/ (HFD+CN1000); dan mencit yang dirawat dengan MECN pada 1500 mg/kg (HFD+CN1500). Semua mencit telah dirawat selama 21 hari. Kajian ini menunjukkan bahawa rawatan MECN pada 1000 dan 1500 mg/kg mengurangkan

berat badan, lemak visera relatif, profil lipid serum, malondialdehid (MDA) dalam otot, kolesterol dan komposisi asid lemak tepu ($P<0.05$). Histologi lemak visera menunjukkan penurunan saiz sel adiposit hipertrofi selepas rawatan dengan MECN berbanding dengan HFDC ($P<0.05$). Ekspresi gen PPARγ hepatik dan SCD1 mRNA telah berkurang, terutamanya pada mencit yang diberi makan 1000 dan 1500 mg/kg MECN berbanding dengan kumpulan HFDC. Mencit yang dirawat dengan MECN pada 1500 mg/kg menunjukkan penurunan ekspresi PPARα, dan peningkatan ekspresi mRNA HSL. Perbandingan adipositokin menunjukkan mencit yang dirawat dengan MECN pada 1000 dan 1500 mg/kg mempamerkan paras adiponektin yang meningkat ($P<0.05$), dan penurunan paras ($P<0.05$) leptin, IL-6, dan TNFα yang ketara berbanding dengan HFDC. Kesimpulannya, keputusan menunjukkan bahawa MECN berupaya mengurangkan obesiti yang disebabkan oleh diet, melalui proses kawalatur ke atas ekspresi gen dan adipositokin yang terlibat dalam metabolisme lipid. Walaubagaimanpun, kajian klinikal yang selanjutnya adalah perlu untuk mengesahkan efikasi klinikalnya.

ACKNOWLEDGEMENTS

All praise is due to Allah and may peace and blessings be upon Mohammed and all his family members and companions. I will be forever grateful to the people in my life who believed in me and who stood by me when all the doors were closed. First, I would like to thank Prof. Dr. Goh Yong Meng, the chairman of my supervisory committee. Also, I have never met a more honest and positive man than Dr. Goh Yong Meng. It was a privilege for me to have Dr. Goh Yong-Meng, Prof. Zailina binti Hashim and Dr. Mahdi Ebrahimi as my co-supervisors and thank them for their advice and suggestions. Without their perceptive supervision and encouragement, this work would not have been accomplished. I would like to express my deepest gratitude to Dr. Mahdi Ebrahimi for his valuable insights, his intellectual, moral support, wisdom and sustenance, as well as giving me the opportunity to continue my PhD study. Acknowledgement also goes to the Ministry of Higher Education and Scientific Research, Kurdistan Regional Government, and the President, Dean and staff of Soran University and Faculty of Education for giving me a study leave. I also wish to express my sincere gratitude to the Dean of the Faculty of Veterinary Medicine and Medicine and Health Science, Universiti Putra Malaysia for their facilities and the unlimited assistance from their staff. I would also like to thank many people who stood beside me, whose names may not be mentioned here. I will never forget them. I am indebted to my parents, sisters and brothers for their unlimited support and patience during my study.

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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LIST OF ABBREVIATIONS

ABST	2-2'-Azinobis 3-ethyl-benzothiazoline -6-sulfonic acid
AchE	Acetylcholinesterase
AGT	Angiotensinogen
ALP	Alkaline phosphate NF-kBROS
Aq.	Gly Aquaglycoporin channels
AST	Aspartate aminotransferase
AT	Adipose tissue
ATGL	Adipose triglyceride lipase
BHA	butylated hydroxyanisole
BHT	butylated hydroxytoluene
BAT	Brown adipose tissue
BM1	Body mass index
C. nutans	*Clinacanthus nutans*
cAMP	Cyclic adenosine monophosphate
CETP	Cholesterol ester transfer protein
COMT	Catechol methyl transferase
cDNA	Complementary DNA
CO_x	Cyclooxygenase-2
CRP	C-reactive protein
CT	Cycle threshold
DPPH	2, 2-Diphenyl-2 picrylhydrazyl hudrate
DG	Diacylglycerol
ELISA	Enzyme-linked immunosorbent assay
ER	Endoplasmic reticulum

FA	Fatty acids
FBR	Foundation for Biomedical Research
G	Gram
G-3-P	Glycerol-3-phosphate
HFD+CN500	High fat diet group treated with 500 mg/kg MECN
HFD+CN1000	High fat diet group treated with MECN at 1000 mg/kg
HFD+CN1500	High fat diet group treated with MECN at 1500 mg/kg
HFD+Orlistat	High fat diet group treated with orlistat
HFDC	High-fat diet control group
HSL	Hormone sensitive lipase
IACUC	Institutional Animal Care and Use Committee
ICAM-1	Intracellular adhesion molecule 1
I.P	Intraperitoneally
I.V	Intravenously
IL-6	Interleukin-6
LDL	Low-density lipoprotein
LDLC	Low density lipoprotein cholesterol
LPL	Lipoprotein lipase.
MCP-1	Monocyte chemoattractant protein 1
MDA	Malondialdehyde
MECN	Methanolic leaf extracts of *Clinacanthus nutans*
MG	Monoacylglycerol
mg/kg	Milligram/ kilogram
mRNA	Messenger ribonucleic acid
MUFA	Monounsaturated fatty acids
NC	Normal diet control

NE	Nor epinephrine
NHMS	National Health and Morbidity Survey
NMDAR	N-methyl-D aspartate receptors
nm	Nanometre
NF-kB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NSAIDs	non-steroidal anti-inflammatory drugs
PA1	Plasminogen activator inhibitor
PCV	Packed cell volume
PPARγ	Peroxisome proliferator-activated receptors γ
RBC	Red blood cell
ROS	Reactive oxygen species
RT-qPCR	Real-time quantitative polymerase chain reaction
SFA	Saturated fatty acid
SDS	Sodium dodecyl sulfate
SCD	Stearoyl-Coenzyme A-Desaturase
SEM	Standard error of mean
SNS	Sympathetic nervous system
$SOCS^3$	Suppressor of cytokine signaling
SREBP	Sterol regulatory element-binding protein
T2DM	Type 2 diabetes mellitus
TBA	Thiobarbituric acid
TBARS	Thiobarbituric acid reactive substances
TG	Triglyceride
TNF-α	Tumor necrosis factor alpha
UCP1	Uncoupling protein 1

UK	United Kingdom
VLDL	Very-low-density lipoproteins
WAT	White adipose tissue
WBC	White blood cell
WHO	World Health Organization

CHAPTER 1

INTRODUCTION

Obesity occurs when the adipose tissue and adipose mass grow dramatically through two mechanisms namely, adipocyte hyperplasia and hypertrophy (Sun *et al*., 2011). Obesity is caused by several factors including diet, inadequate physical activity, dysregulation of the genes and adipocytokines involved in the lipid metabolism. However, the over consumption of fat and decreased physical activity are the most common causes of obesity (Hsu *et al*., 2014). According to the World Health Organization (WHO) obesity is regarded as a disease (Ahmad and Imam, 2016). It is usually accompanied with many serious medical complications, such as hypertension, coronary heart, renal diseases, type 2 diabetes and several forms of cancer such as colon, breast and gastrointestinal cancers (WHO, 2000a; Renehan *et al.*, 2008). Overweight and obesity have been recently found to be the fifth leading cause of deaths worldwide (Amano, 2013). Specifically, their complications account for 100,000 to 400,000 annually (Zawawi, 2011). If no serious actions are taken, obesity may reach the pandemic level in 2040 (Amano, 2013). The development of fat tissues produce different bioactive substances, known as adipocytokines or adipokines, which could cause the development of different metabolic-illnesses that result from the adjusted glucose, lipid homeostasis and inflammatory responses (Dandona *et al*., 2004). Undeniably, adipose tissue has emerged as an endocrine organ which plays a vital role in metabolic regulation and production of adipocytes derivatives involved in both the pro-inflammatory and anti-inflammatory adipocytokines (Wang and Huang, 2015). Obese subjects have been implicated with high levels of pro-inflammatory adipocytokines which are interleukin-6 (IL-6) and tumor necrosis factor (TNFα) and leptin along with decreased production of anti-inflammatory adipocytokines (adiponectin) (Makki *et al*., 2013). The accumulated fat may induce the release of free fatty acids from adipocytes into the circulation, which could be an important factor in the regulation of insulin sensitivity (Dandona *et al*., 2004). The body systems use energy for the maintenance of essential physiological functions (basal metabolic rate) necessary for performing physical activities and for adaptive thermogenesis. Moreover, the body responds to the temperature of the environment, quantity and types of nutrient consumed (Pandey *et al*., 2016). Factors such as gender, growth, age, physical bodily function and body composition affect energy expenditure (Pandey *et al*., 2016). Increased energy consumption combined with diet modification reduces both stored and circulating fat in the body (Rocandio *et al*., 2001). Weight loss through pharmacotherapy treatment can also reduce the hazard to morbidity and mortality (Rudelle *et al*., 2007). Therefore, treating obese people through lifestyle interventions and/or pharmacological therapies is a continued research effort (Rudelle *et al*., 2007). Among the most common pharmacological drugs concurrently used as anti-obesity agent is orlistat (Ferraz *et al*. 2004). It inhibits the gastric and pancreatic lipases and consequently reduces the lipid absorption from the gut and sibutramine that acts as an oral anorexiant (Rudelle *et al*., 2007). The obvious side effects of anti-obesity medicines, such as sibutramine which was associated with myocardial ischemia, have been the reason for the withdrawals of this product from the market in several countries (Mohamed *et al*., 2014). The side effects of synthetic anti-obesity drugs

necessitate the finding of a suitable natural/herbal alternative. The natural products extracted from medicinal plants have been practiced as a folk medicine for a long time (Newman and Cragg, 2012). Herbal drugs have active ingredients in their crude or processed condition, in addition to certain excipients like solvents, diluents or preservatives (Calixto, 2000). Evaluations suggest that some medicinal plants and their extracts can be utilized to prevent diet-induced obesity and thus may reduce weight (Ranjbar *et al*., 2010). A previous work has suggested the effectiveness of *Clinacanthus nutans* Lindau, a plant from the family of Acanthaceae. It is commonly known as Sabah snake grass in Malaysia (Roosita *et al*., 2008). *Clinacanthus nutans* is one of the endemic plants that have proved to have medicinal properties as was evidenced through the traditional use. *Clinacanthus nutans* has important constituents, like phenolics, flavonoids, stigmasterol, β-sitosterol, lupeol, betulin, chlorophyll derivatives, protocatechuic acid, C-glycosyl flavones, vitexin, isovitexin, shaftoside, isomollupentin, 7-*O*-β-gluco pyranoside, orientin, isoorientin, cerebrosides, steroids, triterpenoids, glycerides, monoacylmonogalactosylglycerol and sulfur-containing glucosides (Tu *et al*., 2014; Mustapa *et al*., 2015; Sarega *et al*., 2016a; Alam *et al*., 2016). The phytochemical compounds namely, phenols, tannins, alkaloids, steroids, protocatechuic acid and terpenes, may have the ability to exert hypolipidemic activity (Panmei *et al.*, 2007). Different plant-based polyphenols have been known to quench free radicals and exhibit anti-inflammatory properties, as well as anti-hyperglycemic and anti-hyperlipidemic properties (Nakazato *et al*., 2006; Atanassova *et al*., 2011; Tresserra *et al.,* 2014). Despite all known biological activities in earlier work, as well as its increased general acceptance, this plant is believed to be have the potential to reduce weight and lower blood cholesterol. Nonetheless, such assumptions still required further empirical evidence. The present study aims to investigate this plant by using doses of methanolic leaf extract of *Clinacanthus nutans* (MECN) similar to previous research (Zakaria *et al*., 2016). Recent evidence has shown that MECN improves lipid profiles in rats (Sarega *et al*., 2016a) and can increase the acetylcholinesterase (AchE) activity in the liver and heart (Lau *et al*., 2014), in addition to its powerful anti-inflammatory property in inhibiting the neutrophil responsiveness (Wanikiat *et al*., 2008). Polyphenols have been known to regulate lipid metabolism by inducing metabolic gene expression, or trigger the transcription factors that play a significant part in energy metabolism (Ali *et al*., 2014). There are numerous mechanisms for the reduction of adipogenesis, such as suppression of growth and differentiation of adipocytes by inhibiting the peroxisome proliferator-activated receptor gamma (PPARγ) and sterol regulatory element-binding protein (SREBP2) gene expression (Mayoral *et al.*, 2015; Moseti *et al.*, 2016). Besides, the down regulation of stearoyl-CoA desaturase (SCD) gene can stimulate the insulin sensitivity action, and thus produce effective energy utilization (Karahashi *et al.*, 2013). However, even though the presence of polyphenols in *Clinacanthus nutans* has been determined, there is still little evidence about the anti-obesity properties and the mechanism by which *Clinacanthus nutans* could exert potential anti-obesity effects.

1.2 Problem Statement

Obesity is a severe public health challenges in the 21st century, in Southeast Asia and elsewhere in the world. Obesity is considered one of the primary risk factors for chronic and non-transmissible diseases (Dans *et al*., 2011). There are recent reports which suggest that Malaysia has the highest obesity 13.3% and overweight 38.5% cases in Southeast Asia (AROFIIN, 2017). More specifically, around 60% of the Malaysian aged ≥ 18 has body mass index (BMI) >25 kg/m^2 (Ng *et al*., 2014). Overweight which leads to higher health and economic burdens is today a global challenge (Tuan and Nicklas, 2009). Obese people have been observed to incur about 30% of higher medical costs in comparison with normal weight individuals (Withrow and Alter, 2011). The Asia Roundtable on Food Innovation for Improved Nutrition has reported that obesity accounts for 10 to 19% of the overall healthcare costs in Malaysia, totaling RM 4.26 to 8.53 billion (AROFIIN, 2017). In the USA, similar reports suggest that every American adult will be either overweight or obese by 2048. This will increase the expenditure attributed to obesity, costing USD 860.7 to 956.9 billion or 16 to 18% of the overall US health care expenditure by 2030 (Wang *et al*., 2008). Attempts at treatments via anti-obesity drugs are hampered by their side-effects. In this regard, coming up with a dietary supplementary that could potentially reduce the weight gain is the main concern of the research in the field (Mohamed *et al*., 2014). The increased prevalence of overweight and obesity, in several non-Western countries including Malaysia, has made the demands for alternative approaches to body weight management very necessary. More research endeavors are being investigated for their anti-obesity properties (Rudelle *et al*., 2007). The present study aimed to provide better insights on the toxicity profile of methanolic leaf extract of *Clinacanthus nutans* and the beneficial effects of methanolic leaf extract of *Clinacanthus nutans* against overweight/obesity.

1.3 Significance of the Study

The *Clinacanthus nutans* has been used as a traditional medicine to treat diseases like skin rashes, scorpion and insect bites, diabetes mellitus and many more other diseases in Southeast Asia, particularly in Malaysia, Indonesia and Thailand (Tuntiwachwuttikul *et al*., 2003; Sakdarat *et al*., 2009; Alam *et al*., 2016). Many recent investigations have revealed that this plant holds great promise for health and disease prevention. This has brought a lot of attention on how this plant would contribute in health management. The findings of this research are hoped to provide insights into the effect of *Clinacanthus nutans* on physiological and biochemical changes in obese mice. The outcome of this work can be exploited to produce a new supplement from natural plant to treat or prevent obesity phenotype and its complications in future.

1.4 Research Objectives

1.4.1 General Objective

The main objective of the study was to investigate the potential anti-obesity effects of crude methanolic leaf extract of *Clinacanthus nutans* (MECN) on high-fat diet-induced obese mice.

1.4.2 Specific Objectives

The specific objectives of this study were:

1- To identify the total phenolic and flavonoid contents, and antioxidant activities of methanolic leaf extract of *Clinacanthus nutans* (MECN).
2- To determine the potential toxic effects of MECN treatment in mouse model with respect to the hematological, biochemical and histopathological parameters after oral administration for 28 days.
3- To investigate the effects of MECN treatment on body weight, adipose cellularity, biochemical parameters and lipid profile in obese mice fed a high-fat diet.
4- To examine the effects of MECN treatment on gene expressions of PPARα, PPARγ, HSL, SCD and SREBP mRNA, as well as adipocytokines including adiponectin, leptin, IL-6 and TNF regulation in obese mice fed a high-fat diet.

1.4.3 Hypothesis

It was expected that: sub-acute oral toxicity study of MECN at 1500 mg/kg or lower is safe in mice. MECN would affect adipose cellularity, lipid profiles, biochemical parameters, mRNA expression levels of the different genes and adipocytokines on a high-fat diet-induced obese mice.

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