



UNIVERSITI PUTRA MALAYSIA

***THERAPEUTIC EFFECTS OF *Cosmos caudatus* Kunth LEAF
EXTRACT IN THE PREVENTION AND TREATMENT OF OBESITY
IN SPRAGUE DAWLEY RATS***

HAFEEZDA BINTI ABDUL RAHMAN

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**This thesis submitted to the School of Graduate Studies, Universiti Putra
Malaysia, in Fulfillment of the Requirements for the Degree of Doctor
of Philosophy**

May 2015

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

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Faculty : Food Science and Technology

Obesity is a common nutritional disorder that has become one of the most important health issues of modern society around the world. Accumulating studies have shown that various herbs can be good sources of potent antioxidants. However, little information is available on the anti-obesity potential of these herbs. Preliminary study was carried out to investigate the anti-obesity and antioxidant activity of 8 common herbs, namely *Cosmos caudatus*, *Pluchea indica*, *Lawsonia inermis*, *Carica papaya*, *Piper betle*, *Andrographis paniculata*, *Pereskia bleo* and *Melicope lunu*. Anti-obesity activity was assessed using inhibition of pancreatic lipase (PL) and lipoprotein lipase (LPL) activity whereas antioxidant activity was measured using free radical DPPH (2,2-diphenyl-2-picrylhydrazyl) scavenging activity. Results of the preliminary study revealed that *C. caudatus* exhibited good anti-obesity activity as well as excellent antioxidant activity. Therefore, *C. caudatus* was selected for further study by extraction with different concentrations of ethanol (100%, 80%, 60%, 50% and 40%). Hundred percent ethanol extracts of *C. caudatus* showed highest activity in both anti-obesity (21.8±1.5% and 19.9±1.1% in pancreatic and lipoprotein lipase assay) and antioxidant activity (24.9±1.1 µg/mL) with total phenolic content of 865.8±5.0 mg GAE/g extract and total flavonoid content of 398.8±34.8 mg RE/g extract compared to that of other extracts. Strong positive correlation between antioxidant activity (DPPH) and both phenolic ($r = 0.708$) and flavonoid ($r = 0.766$) content was observed. The same trend existed between anti-obesity (PL and LPL) and that of phenolic ($r = 0.935$, 0.845) and flavonoid ($r = 0.945$, 0.835) compounds respectively. The extract consisted of various flavonoids (quercetin, quercitrin, catechin, epicatechin, kaempferol, rutin, and chlorogenic acid) as identified by nuclear magnetic resonance (NMR), liquid chromatography mass spectroscopy (LC-MS), and high performance liquid chromatography (HPLC). Based on the results obtained, 100% ethanol extract of *C. caudatus* was further assessed for the preventive and therapeutic effects of

obesity *in vivo*. In the preventive study, *C. caudatus* extract (175 mg/kg and 350 mg/kg body weight) was given to the lean *Sprague dawley* rats fed with high fat diet (HFD) for 11 weeks whereas in the treatment study, obese rats were treated with *C. caudatus* extract (200 mg/kg and 400 mg/kg body weight) for 9 weeks. In the preventive study, the extracts significantly suppressed the increase in body weight gain by 33.0 - 42.5% and percentage of abdominal fat by 33.0 - 42.0% when compared to that of control HFD group. However, it failed to reduce the weight and percentage of abdominal fat in HFD induced obese rats. Nevertheless, for both experiments the extract significantly suppressed the increase of plasma triglycerides, total cholesterol, LDL, insulin and leptin level. In addition, plasma ghrelin and adiponectin levels were increased. The extract also increased the fecal excretion of fat in rats (96.9±10.5 - 114.6±9.3 mg/g in preventive study and 87.7±10.0 - 124.6±20.2 mg/g in treatment study) when compared to that of control HFD groups (55.4±6.6 - 58.2±2.6 mg/g) respectively, suggesting that *C. caudatus* reduces the progression of obesity by inhibiting pancreatic lipase, leading to malabsorption of fat, validating the *in-vitro* results obtained in first part of the study. In the final part of the study, both urine and serum metabolites of rats were analyzed using (NMR) spectroscopy and multivariate data analysis (MVDA). Lean and obese rats were clearly discriminated from each other on Orthogonal partial least square (OPLS-DA) score plot proving the ability of the high fat diet used in inducing obesity. Metabolites associated with lipid, tricarboxylic acid cycle (TCA), glucose, amino acid, creatine and gut microbiota metabolism were found to be responsible for the discrimination observed. Interestingly, the therapeutic effects of *C. caudatus* extracts, specifically the low dose (200 mg/kg) were found to be better than that of Orlistat, based on the fact that the metabolic profiles of *C. Caudatus* treated groups were very similar to that of normal group. Betaine, succinate, 3-hydroxybutyrate, creatine, glycine, *N*-acetylglycine, pyruvate and glutamine were significantly increased/decreased towards the normal level. Finally, partial least square analysis (PLS-DA) showed that the obese group moved away from the position of lean group and after 9 weeks of treatment both treated groups were regulated back closer towards their healthy baseline levels, confirming the therapeutic effects of the extracts obtained from biochemical assays measured in the previous chapter. This study showed the anti-obesity effects of *C. caudatus* through inhibition of lipase activity as demonstrated by the increase in fecal fat content and also the positive effects on other obesity biomarkers measured. It also successfully demonstrated the ability of NMR based metabolomics in unraveling therapeutic effects of *C. caudatus* and further provides biochemical insights into the metabolic alterations associated with obesity. Results of the study suggest that *C. caudatus* has potential as a natural supplement or functional ingredient for the prevention and treatment of obesity.

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

**KESAN TERAPEUTIK EKSTRAK DAUN *Cosmos caudatus* Kunth
DALAM RAWATAN PENCEGAHAN DAN PEMULIHAN OBESITI
TERHADAP TIKUS SPRAGUE DAWLEY**

Oleh

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Obesiti adalah gangguan pemakanan biasa yang telah menjadi salah satu isu kesihatan yang paling penting dalam masyarakat moden di seluruh dunia. Kajian terkumpul telah menunjukkan bahawa pelbagai herba boleh menjadi sumber antioksidan yang baik. Walau bagaimanapun, hanya sedikit maklumat didapati pada potensi anti-obesiti herba ini. Kajian awal telah dijalankan untuk menyiasat aktiviti anti-obesiti dan antioksidan 8 herba, iaitu *Cosmos caudatus*, *Pluchea indica*, *Lawsonia inermis*, *Carica papaya*, *Piper betle*, *Andrographis paniculata*, *Pereskia bleo* dan *Melicope lunu*. Keputusan kajian menunjukkan bahawa *C. Caudatus* menunjukkan aktiviti anti-obesiti serta antioksidan yang sangat baik. Aktiviti anti-obesiti dinilai menggunakan perencatan lipase pankreas (PL) dan lipase lipoprotein (LPL) aktiviti manakala aktiviti antioksidan dinilai menggunakan pemerangkapan radikal bebas DPPH (2,2-difenil-2-picrilhidrazil). *C. caudatus* telah dipilih untuk kajian lanjut oleh pengekstrakan etanol dengan kepekatan yang berbeza (100%, 80%, 60%, 50% dan 40%). Seratus peratus ekstrak etanol daripada *C. caudatus* menunjukkan aktiviti paling tinggi dalam kedua-dua aktiviti iaitu anti-obesiti ($21.8 \pm 1.5\%$ and $19.9 \pm 1.1\%$ dalam aktiviti pankreas dan lipoprotein lipase) dan antioksidan ($24.9 \pm 1.1 \mu\text{g/mL}$) dengan jumlah kandungan fenolik sebanyak $865.8 \pm 5.0 \text{ mg GAE/g}$ ekstrak dan jumlah kandungan flavonoid sebanyak $398.8 \pm 34.8 \text{ mg RE/g}$ ekstrak berbanding dengan ekstrak lain. Korelasi positif yang kuat antara aktiviti antioksidan (DPPH) dan kedua-dua kandungan fenolik ($r = 0.708$) dan flavonoid ($r = 0.766$) diperhatikan. Trend yang sama wujud antara anti-obesiti (PL dan LPL) dan juga fenolik ($r = 0.935$, 0.845) dan flavonoid ($r = 0.945$, 0.835). Ekstrak ini terdiri daripada pelbagai flavonoids (kuersetin, kuersitrin, katekin, epikatekin, kaemferol, rutin dan asid klorogenik) dikenal pasti oleh resonans magnetik nuklear (NMR), cecair kromatografi spektroskopi jisim (LC-MS), dan kromatografi cecair berprestasi tinggi (HPLC). Berdasarkan keputusan yang diperolehi, 100% ekstrak etanol daripada *C. caudatus* terus dinilai untuk kesan pencegahan dan terapeutik

obesiti pada tikus *Sprague dawley* diberi makan diet lemak yang tinggi. Dalam kajian pencegahan, ekstrak *C. caudatus* (175 mg/kg dan 350 mg/kg berat badan) telah diberikan kepada tikus normal yang diberi makan dengan diet yang tinggi lemak selama 11 minggu manakala dalam kajian rawatan, tikus obes telah dirawat dengan ekstrak *C. caudatus* (200 mg/kg dan 400 mg/kg berat badan) untuk 9 minggu. Dalam kajian pencegahan, ekstrak berjaya menghalang peningkatan berat badan sebanyak 33.0 - 42.5% dan peratusan lemak sebanyak 33.0 - 42.0% di bahagian abdomen pada kumpulan yang dirawat berbanding kumpulan HFD kawalan. Walau bagaimanapun, ia gagal untuk mengurangkan berat badan dan peratusan lemak di bahagian abdomen tikus obes. Bagi kedua-dua kajian, ekstrak berjaya mengurangkan peningkatan trigliserida, jumlah kolesterol, LDL, insulin dan leptin. Di samping itu, paras grelin dan adiponektin juga meningkat. Ekstrak ini juga meningkatkan perkumuhan lemak dalam tinja tikus yang dirawat (96.9 ± 10.5 - 114.6 ± 9.3 mg/g dalam kajian pencegahan dan 87.7 ± 10.0 - 124.6 ± 20.2 mg/g dalam kajian rawatan) berbanding kumpulan HFD kawalan (55.4 ± 6.6 - 58.2 ± 2.6 mg/g) masing-masing, menunjukkan bahawa *C. caudatus* mengurangkan perkembangan obesiti dengan menghalang aktiviti lipase pankreas, yang membawa kepada kekurangan penyerapan lemak, mengesahkan keputusan in-vitro yang didapati di bahagian pertama kajian. Dalam bahagian akhir kajian ini, kedua-dua urin dan serum metabolit tikus telah dianalisis dengan menggunakan (NMR) spektroskopi dan analisis data multivariat (MVDA). Tikus normal dan obes jelas didiskriminasi antara satu sama lain pada ortogonal separa kurangnya persegi (OPLS-DA), membuktikan keupayaan diet lemak tinggi yang digunakan dalam mendorong obesiti. Metabolit yang berkaitan dengan lipid, kitaran asid trikarboxylic, glukos, asid amino, kreatin dan metabolisma microbiota usus didapati bertanggungjawab untuk diskriminasi yang diperhatikan. Menariknya, kesan terapeutik ekstrak *C. caudatus*, khususnya dos yang rendah (200 mg/kg) didapati lebih baik daripada Orlistat, berdasarkan fakta bahawa profil metabolik tikus yang dirawat *C. caudatus* adalah hampir sama dengan kumpulan normal. Betaine, sukinat, 3-hydroxybutyrate, kreatin, glicin, N-acetylglicin, piruvat dan glutamin telah meningkat/menurun dengan ketara ke arah tahap yang normal. Akhirnya, sebahagian analisis persegi kurangnya (PLS-DA) menunjukkan bahawa kumpulan yang obes beralih daripada kedudukan kumpulan normal dan selepas 9 minggu rawatan kedua-dua kumpulan dirawat bergerak lebih dekat ke arah tahap asas sihat mereka, mengesahkan kesan terapeutik ekstrak diperolehi daripada asai biokimia yang diukur dalam bab sebelumnya. Kajian ini menunjukkan kesan anti-obesiti *C. caudatus* melalui perencatan aktiviti lipase seperti yang ditunjukkan oleh peningkatan dalam kandungan lemak tinja dan juga kesan positif pada penanda biologi obesiti lain yang diukur. Ia juga berjaya mempamerkan keupayaan metabolik berasaskan NMR untuk menunjukkan kesan terapeutik *C. caudatus* dan seterusnya memberikan pandangan biokimia ke dalam apa-apa perubahan metabolik yang berkaitan dengan obesiti. Keputusan kajian menunjukkan bahawa *C. caudatus* berpotensi sebagai makanan tambahan semula jadi atau bahan berfungsi untuk mencegah dan merawat obesiti.

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This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfillment 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

ACC	Acetyl-CoA Carboxylase
ACE	Angiotensin Converting Enzyme
ACUC	Animal Care and Use Committee
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AMPK	Monophosphate-Activated Protein Kinase
ANOVA	Analysis of variance
APOC-II	Apolipoprotein C II
AST	Aspartate Aminotransferase
BAT	Brown Adipose Tissue
BHA	Butylated hydroxyanisole
BHT	Butylated hydroxytoluene
BMI	Basal Metabolic Rate
BSA	Bovine Serum Albumin
CEBP- α	Cancer Enhancer Binding Protein - Alpha
cm	Centimetre
CNTF	Ciliary Neurotrophic Factor
d	Doublet
dd	Doublet of Doublets
DPPH	1,1-diphenyl-2-picrylhydrazyl
ECG	Epicatechin Gallate
EGC	Epigallocatechin
EGCG	Epigallocatechin Gallate
EL	Endothelial Lipase
FDA	Food and Drug Administration
FFA	Free Fatty Acid
FTC	Ferric Thiocyanate
g	Gram
GA	Gallic Acid
GAE	Gallic Acid Equivalent
GGT	Ggamma-glutamyl Transferase
GhR	Ghrelin Receptor
GSE	Grape Seed Extract
HCA	Hydroxycitric Acid
HCL	Hydrochloric Acid
HFD	High Fat Diet
HL	Hepatic Lipase
$^1\text{H-NMR}$	Proton nuclear magnetic resonance
HPLC	High Performance Liquid Chromatography
HZ	Hertz
IC ₅₀	Inhibition Concentration at 50 Percent
IDL	Intermediate Density Lipoprotein
J	Coupling constant in Hz
JAK/STAT	Janus Kinase/Signal Transducer
Kg	Kilogram
L	Litre

LCMS	Liquid Chromatography – Mass Spectroscopy
LDL	Low density lipoprotein
LPL	Lipoprotein Lipase
m	Multiplet
mg	Milligram
min	Minute
mL	Millilitre
mL	Micro litre
mm	Millimetre
mRNA	Messenger Ribose Nucleic Acid
MVDA	Multivariate Data Analysis
NADPH	Nicotinamide Adenine Dinucleotide Phosphate
NAOD	Sodium Deuterioxide
ND	Normal Diet
NHMS	National Health and Morbidity Survey
nm	Nanometer
NPY	Neuropeptide Y
OPLS-DA	Orthogonal Partial Least Square Data Analysis
PAI-1	Plasminogen Activator Inhibitor Type 1
PC	Principal Component
PL	Pancreatic Lipase
PLS-DA	Partial Least Square Data Analysis
PPAR	Peroxisome Proliferator Activated Receptor
PPM	Part Per Million
RE	Rutin Equivalent
ROS	Reactive oxygen species
rpm	Revolution per minute
s	Singlet
SOD	Superoxide dismutase
SPSS	Statistical Package for Social Science
TBA	Thiobarbituric Acid
TC	Total Cholesterol
TFC	Total flavanoid content
TG	Triglyceride
TNF- α	Tumor Necrosis Factor- α
TPC	Total phenolic content
TSP	Trimethylsilanepropionic Acid Sodium Salt
UV	Ultraviolet
VLDL	Very Low Density Lipoprotein
WAT	White Adipose Tissue
WHO	World Health Organization
δ	Chemical Shift in ppm
μ g	Microgram
μ m	Micro meter
$^{\circ}$ C	Degree Celsius

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CHAPTER 1

GENERAL INTRODUCTION

Obesity is a leading cause of death worldwide, affecting not only developed but also developing countries. Globally, it is estimated that over 1.4 billion adults are overweight with almost 500 million obese (WHO, 2013). The problem of obesity in Malaysia is at an alarming stage. Reports from the National Health and Morbidity Surveys (NHMS) in 1996, 2006 and 2011 respectively, showed that the prevalence of obesity among adults were increased by three-fold from 4.4% to 14% and 15.1% within 15-years period (NHMS 1996, NHMS 2006, NHMS 2011). Latest study showed that Malaysia is Southeast Asia's most obese country with 49% women and 44% men were either obese or overweight (Ng *et al.*, 2014). Looking at the statistics, scientists are searching for better approach to further understand the diseases and therefore can help in early detection, prevention, and offer solution for effective treatment to this ever-escalating problem.

Malaysia is a tropical country rich with medicinal plants and herbs. In Malaysia and other parts of the world, these medicinal herbs have long been used in the treatment of various ailments. As research on obesity and the use of pharmaceutical drugs in management of obesity is highly controversial and does not provide effective long-term solution, the role of medicinal herbs for treatment of obesity has gained much interest.

Cosmos caudatus, locally known as 'Ulam raja' is a well known herbs found mostly in all tropical regions including Mexico, Central and South America, Malaysia, Thailand and Indonesia (Samy *et al.*, 2005). In Malaysia, it is often consumed raw as salad with rice and food flavouring due to its unique taste and aroma (Shui *et al.*, 2005). Traditionally, it has been used to improve blood circulation, promote the formation of healthy bones, reduce body heat, promote fresh breath, treat infections associated with pathogenic microorganisms, lower high blood pressure and also useful in cleansing the blood (Burkill, 1966; Ismail, 2000; Shui *et al.*, 2005; Hassan 2006; Bodeker, 2009). This herb is also known to possess antioxidant, anti-diabetic, anti-hypertensive, anti-bacteria and anti-fungal properties (Rahalison *et al.*, 1991, Shui *et al.*, 2005, Rasdi *et al.*, 2010, Loh and Hadira, 2011).

Metabolomic approach has been shown to be able to distinguish the different phenotypes and discover potential biomarkers associated with certain phenotypes (Kim *et al.*, 2011). This is made possible with the help of high-throughput tool such as NMR. NMR-based metabolomics can provide a snapshot of metabolites and allow comprehensive metabolite profiling of body fluids. Moreover, it is nondestructive, compatible to both liquid and solid samples and requires no derivatisation with only little sample preparation steps required, making it the perfect tool for collecting a

wealth of data sets (Verpoorte *et al.*, 2007). With these benefits and abilities, metabolomics has become an invaluable tool in finding new biomarkers in obesity research and finally help in identifying mechanisms of obesity. This approach not only identifies, but also quantifies all metabolites in biological system in response to physiological or genetical modifications.

The metabolic effects of polyphenolic rich herbs are commonly assessed in animal studies and clinical trials by measuring plasma or serum concentrations of lipids, glucose, and other biochemical assays. However results are often inconsistent and do not reflect the overall effects of the herbs. Metabolomics provide better understanding on the effects of diet intervention on the metabolism with a holistic approach. This approach will allow for better understanding in terms of the mechanism of action and also help to identify biomarkers of effects that may not be possible with conventional methods (Scalbert *et al.*, 2005, Rezzi *et al.*, 2007). Therefore, to discover biomarkers associated with obesity and *C. caudatus* treatment, both conventional biochemical assays and ¹H-NMR based metabolomics approach was used to study the metabolic changes occurring in the urine and serum of obese rats fed a high fat diet and consequently treated with *C. caudatus* extracts. The combination of both traditional biochemical assay and ¹H-NMR based metabolomics will be able to give the more indepth picture in understanding the disease, evaluate the progression, determining the safety and efficacy of therapeutic interventions and also reveal the potential biomarkers altered with obesity and its treatment.

Hence, the objectives of this study were:

1. To determine the anti-obesity, antioxidant activity, phenolic and flavonoid content of *C. caudatus* extracted with different concentration of ethanol (100, 80, 60, 50 and 40%).
2. To determine the preventive effects of *C. caudatus* leaf extract on lean rats fed a high fat diet.
3. To determine to treatment effects of *C. caudatus* leaf extract on high fat diet induced obese rats.
4. To investigate the metabolic abnormalities in high fat diet induced obese rats and the metabolic alterations associated with the therapeutic effects of *C. caudatus* leaf extract using metabolomics approach.

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