



UNIVERSITI PUTRA MALAYSIA

**ANTIOXIDANT AND ANTI-OBESITY PROPERTIES OF SELECTED
LOCAL CHILI VARIETIES *IN VITRO***

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By

CHAN SUK HUEI

**Thesis submitted to the School of Graduate Studies, Universiti Putra
Malaysia, in Fulfillment of the Requirement for the Degree of Master of
Science**

September 2019

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Abstract of thesis to the Senate of Universiti Putra Malaysia in fulfillment of the requirement for the degree of Master of Science

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September 2019

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Obesity is a complex metabolic disease caused by positive energy balance, which leads to an increase in body fat mass. Currently, obesity is a health concern as it may initiate common chronic diseases. Among Malaysians, almost half of the population is overweight or obese. Chili pepper is an important spice that brings spiciness and commonly used in Malaysian cuisines. In the previous studies conducted, chili pepper has been reported to have strong antioxidant and anti-obesity properties. However, the antioxidant and anti-obesity properties of chili varieties in Malaysia has not yet been fully investigated. This study was carried out to determine antioxidant properties (content and activity) and anti-obesity properties among chili pepper varieties in Malaysia. In the current study, seed, pulp, and whole fruit parts were separated from five different common varieties of chili peppers in Malaysia (*Cili Kulai 151*, *Cili Kulai 568*, *Cili Bara*, *Cili Centil*, and *Cili Pelita*). The total phenolic content (TPC) and total flavonoid content (TFC) of all ethanolic extracts of chili peppers were determined. The antioxidant activities of the extracts were determined through Ferric-Reducing Antioxidant Power (FRAP) and 2,2'-azinobis-(3-ethyl-benzothiazoline-6-sulphonic acid (ABTS) assays. The extracts with the highest antioxidant activity from each part of chili (seed, pulp, whole fruit) undergone HPLC analysis for quantification of capsaicin. Cell cytotoxicity of the selected chili extracts was determined in 3T3-L1 preadipocytes using MTT assay. Whereas the ability to inhibit oil accumulation in fully differentiated 3T3-L1 adipocytes of the selected chili pepper extracts was assayed using Oil Red O staining. Inhibition of pancreatic lipase activity was determined spectrometrically. The results showed that *Kulai 568* pulp extract had the highest level of TPC (47.88 ± 0.220 mg GEA/g), whereas *Centil* pulp extract had the highest level of TFC (26.60 ± 0.52 mg QE/g). In term of antioxidant activities, *Bara* pulp extract had the highest value in FRAP (3.058 ± 0.002 mM Fe^{2+} /mg extract) and ABTS ($IC_{50} = 12.411 \pm 0.025$) assays. The level of antioxidant content is strongly and positively correlated with antioxidant activities. Through HPLC analysis, *Bara* pulp extract showed the highest level of capsaicin (72.271 ± 0.957 μ g/ml). Through MTT assay, the results showed the treatment time and dose-dependent properties of the chili extracts. *Centil* seed extract presented the best result in terms of

inhibition of oil accumulation (69.09 – 92.20%), whereas *Bara* pulp extract inhibited the most pancreatic lipase activity ($IC_{50} = 4.84 \pm 0.57 \mu\text{g/ml}$). Thus, it is suggested that *Centil* seed and *Bara* pulp extracts can be a potent antioxidant and anti-obesity agents for prevention of chronic diseases caused by free radicals and obesity treatment.



Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Master Sains

CIRI ANTIOKSIDAN DAN ANTI-OBESITI VARIETI CILI TEMPATAN TERPILIH SECARA *IN-VITRO*

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Obesiti merupakan satu jenis penyakit metabolik yang kompleks disebabkan oleh keseimbangan tenaga positif, yang membawa peningkatan jisim lemak badan. Pada masa ini, obesiti adalah ancaman kesihatan kerana ia merupakan pemulaan kepada penyakit kronik. Di Malaysia, lebih kurang separuh daripada penduduk mengalami masalah berlebihan berat badan. Cili merupakan rempah penting yang membawa kepedasan dan biasanya diguna dalam pelbagai masakan Malaysia. Dalam kajian-kajian terdahulu, cili telah dilaporkan mempunyai sifat antioksidan dan anti-obesiti yang kuat. Walau bagaimanapun, sifat antioksidan dan anti-obesiti antara jenis cili di Malaysia belum pernah dikaji dengan sepenuhnya. Kajian ini dijalankan untuk menentukan ciri antioksidan (kandungan dan aktiviti) dan sifat anti-obesiti antara jenis cili tempatan di Malaysia. Dalam kajian ini, bahagian biji, pulpa dan keseluruhan buah dipisahkan daripada lima jenis cili tempatan yang berbeza (*Cili Kulai 151*, *Cili Kulai 568*, *Cili Bara*, *Cili Centil*, and *Cili Pelita*) telah digunakan. Jumlah kandungan fenolik (TPC) dan jumlah kandungan flavonoid (TFC) dalam kesemua ekstrak etanol cili telah ditentukan. Aktiviti antioksidan ekstrak-ekstrak cili telah ditentukan melalui ujian kuasa antioksidan termasuk penurunan ferum (FRAP), dan ujian 2,2'-azinobis-(3-ethyl-benzothiazoline-6-sulphonic acid (ABTS). Ekstrak yang mempunyai antioksidan tertinggi daripada bahagian berbeza (biji *Centil*, pulpa *Bara*, keseluruhan buah *Kulai 568*) telah menjalani analisis HPLC untuk menentukan kandungan capsaicin. Sitotoksiti dalam sel lemak 3T3-L1 oleh ekstrak cili terpilih telah ditentukan melalui ujian MTT. Manakala keupayaan ekstrak cili tersebut untuk menghalang pengumpulan minyak dalam sel lemak 3T3-L1 telah ditentukan menggunakan pewarnaan Minyak Merah O. Penghambatan aktiviti pankreatik lipase telah ditentukan secara spektrofotometri. Hasil kajian menunjukkan bahawa ekstrak keseluruhan buah *Kulai 568* mempunyai tahap TPC tertinggi, manakala ekstrak pulpa *Centil* mempunyai tahap TFC tertinggi. Dari segi aktiviti antioksidan, ekstrak pulpa *Bara* menunjukkan nilai tertinggi dalam ujian FRAP ($3.058 \pm 0.002 \text{ mM Fe}^{2+}/\text{mg extract}$) dan ujian ABTS ($\text{IC}_{50} = 12.411 \pm 0.025$). Tahap kandungan antioksidan adalah berkorelasi secara kuat dan positif dengan aktiviti antioksidan. Melalui analisis HPLC, ekstrak pulpa *Bara* menunjukkan kandungan capsaicin tertinggi

(72.271±0.957µg/ml). Melalui ujian MTT, membuktikan sifat ekstrak cili bergantung kepada masa rawatan dan dos. Ekstrak biji *Centil* mempamerkan hasil terbaik dari segi penghampatan pengumpulan minyak (69.09 – 92.20%), manakala ekstrak pulpa *Bara* menghalang aktiviti pankreatik lipase yang paling tinggi (IC₅₀= 4.84± 0.57µg/ml). Oleh itu, ekstrak biji *Centil* dan pulpa *Bara* merupakan agen antioksidan dan anti-obesiti yang berpotensi tinggi bagi mengelakkan penyakit kronik yang disebabkan oleh radikal bebas dan rawatan obesiti.



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LIST OF ABBREVIATIONS

WHO	World Health Organization
BMI	Body Mass Index
OECD	Organisation for Economic Co-operation and Development
FDA	Food and Drug Administration
MANS	Malaysian Adult Nutrition Survey
RNI	Reference Nutrient Intake
EMA	European Medicines Agency
BHT	Butylated hydroxytoluene
BHA	Butylated hydroxyanisole
HPLC	High Performance Liquid Chromatography
TPC	Total Phenolic Content
TFC	Total Flavonoids Content
FRAP	Ferric-reducing Antioxidant Power
ABTS	2,2'-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid)
ORO	Oil Red O
<i>C. annuum</i>	<i>Capsicum annuum</i>
<i>C. frutescens</i>	<i>Capsicum frutescens</i>
<i>C. baccatum</i>	<i>Capsicum baccatum</i>
<i>C. chinense</i>	<i>Capsicum chinense</i>
<i>C. pubescens</i>	<i>Capsicum pubescens</i>
MARDI	Malaysian Agricultural Research and Development Institute
ROS	Reactive Oxygen Species
STAT	Signal Transducer and Activator of Transcription
NF- κ B	Nuclear Factor kappa β
AP-1	Activator Protein-1
5-FU	5-fluorouracil
CCA	cholamgiocarcinoma
CLGI	Chronic Low-grade Inflammation
LPS	lipopolysaccharides
GDPH activity	glycerol-3-phosphate dehydrogenase activity
PPAR γ	Peroxisome proliferator-activated receptors gamma
C/EBP α	CCAAT/enhancer-binding protein alpha
KKAgamma	KKA gamma
TRPV1 receptor	Transient receptor potential cation channel subfamily V member 1
HFD	High-Fat Diet
THP	pirarubicin
RDA	Recommended Dietary Allowance
NHMS	National Health and Morbidity Survey
BMR	basal metabolism rate
PUFA	polyunsaturated fatty acids
GAE	Gallic Acid Equivalents
QE	Quercetin equivalent
ABTS \bullet +	ABTS radical cation
DMEM	Dulbecco's Modified Eagle's Medium

CO ₂	Carbon dioxide
MDI	Multi Daily Insulin
IBMX	3-isobutyl-1-methylxanthine
DMSO	Dimethyl sulfoxide
FBS	Fetal Bovine Serum
PS	Penicilin-streptomycin
PBS	Phosphate-buffered saline
MOPS	(morpholinepropanesulphonic acid)
EDTA	Ethylenediaminetetraacetic acid
p-NPB	p-nitrophenylbutyrate
CRD	completely randomized design



CHAPTER 1

INTRODUCTION

1.1 Research background

Obesity is a complex disease caused by the interaction of a myriad of genetic, dietary, lifestyle, and environmental factors, which favors a chronic positive energy balance, and leads to increased body fat mass (Mohamed et al., 2014). According to the definition of the World Health Organization (WHO), obesity can be defined as abnormal or excessive fat accumulation in the body that may bring risk to health. A person is considered as obese when his or her BMI (kg/m^2) value is equal or exceeds 30.

Nowadays, obesity is a worldwide health concern as it is a risk factor for many common chronic diseases including heart disease and stroke, diabetes mellitus, osteoarthritis (OA), and hypertension. According to the topic of 'Obesity Update 2017', Organisation for Economic Co-operation and Development (OECD) found that there is a steady increasing trend in obesity rates until at least 2030. In the year 2014, a study published by in The Lancet said that Malaysia was rated the highest (45.3%) in Asia for obesity. At the same time, the National Health and Morbidity Survey of 2015 reported that almost half of Malaysia population is either overweight or obese.

A review of Chandra et al. (2015) showed that most of the plant extract is safe for human consumption. Currently, natural occurring phytochemicals from plant extracts does provides several possible anti-obesity mechanism such as inhibits adipogenesis, thermogenesis, inhibits pancreatic lipase activity and controls appetite (Yun, 2010). Therefore, the usage of plant extracts may reduce the application of cozy synthetic drugs as a potent therapeutic agent in the future.

Chili pepper, a plant that belongs to the genus of *Capsicum*, is an important spice that is widely used in Malaysian cuisines. Except for its usage as a cooking ingredient, they are also used as an analgesic agent for chronic pains (Bosland and Votava, 2000). Some recent studies on chilies peppers has focused on their beneficial functions as potential antioxidant agent (Mori et al., 2006; Ezekial et al., 2014), anti-hypertensive agent (Chularojmontri et al., 2011), anti-obesity agent (Hsu et al., 2007; Janssens et al., 2014; Mehmet et al., 2015) due to the activities of the unique active components, called as capsaicin and capsaicinoids.

N-Vanillyl-8-methyl-6-(E)-noneamide, or Capsaicin, is the major active component from the group component of capsaicinoids. This is a unique component that existed in *Capsicum* genus (Meghvansi et al., 2010). The presence of capsaicin in chili is determined by a major gene, but it is the action of polygenes acting in a cumulative

manner that determines the various degrees of pungency.

1.2 Problem statements

According to the study of global disease in the year 2013, it was reported that almost half of the adult population in developing countries, such as Malaysia were categorized as overweight and obese. The occurrence of overweight and obesity was found higher among adult women (Ng et al., 2014). In the year 2014, the second Malaysian Adult Nutrition Survey (MANS) showed the increment in the overweight and obese population compared to MANS 2003. The overweight population increased from 26.7% to 32.4%, while obese population increased from 12.2% to 18.5%. Meanwhile, underweight and normal populations were decreased from 9.0% to 6.2% and 52.1% to 42.9% respectively. From the changes in nutritional status among Malaysian, it was observed that the overall body weight increased compared to 2003.

Obesity is caused by excessive energy storage in fat cells through abnormal energy metabolism in the body. It is also the main risk factor for several metabolic diseases (de la Garza et al., 2011). The intake of high fatty and/ or high carbohydrate foods can increase the number of fat cells and also increase their weight, causing obesity. As reported in MANS 2014, there is an increment in percentage contribution of daily energy intake from fat compared to MANS 2003. Therefore, the increased overweight and obese population in Malaysia may due to the increased consumption of fatty food.

However, the options for weight management remain quite limited. Fad diet, a type of diet practice which claims that it can reduces weight in a short period by extremely restricting to a certain type of food without any necessity of exercise. For example, low-carbohydrate and high protein diet, low-carbohydrate and high-fat diet, and low energy diet respectively (Lagiou et al., 2012). They may work on a short-term basis. In fact, these practices will bring harm to a person's health if maintain for long-term basis and does not generally produce marked or sustainable weight loss (Dansinger et al., 2005; LeBlanc et al., 2011).

Weight loss surgery such as bariatric surgery is only suggested for patients with severe obesity, especially when implementation of dietary changes and physical activities does not produce significant weight loss (Pories, 2008, Kang & Park, 2012). It is effective in term of weight loss but this will also bring surgical complications and the frequent need for reoperation to the patient (Melnikova and Wages, 2006; Field et al., 2009). Due to difficulty in eating and nutrient absorption, patients also need to carefully monitor their nutrients state by taking lifelong vitamin supplements (Guth & Murali, 2017).

Since the last decade, most of the approved and marketed anti-obesity drugs such as phentermine, sibutramine and rimonabant have been withdrawn due to serious health issues (Kang et al. 2012). Examples of health issues are such as increased risk of cardiovascular diseases, hypertension, constipation and depression (Christensen et al.,

2007; James et al, 2010, Zhou et al., 2012). In present, orlistat is the only weight loss agent approved by FDA for long-term clinical use in Europe due to its safety for cardiovascular operations and positive effect on diabetic control, although it does not produce effective weight loss (Kang & Park, 2012).

Reduction of dietary fat absorption through inhibition of pancreatic lipase becomes an effective approach in the management of obesity (Bray & Ryan, 2007). Orlistat, the saturated derivative of lipstatin, which is isolated from the bacterium *Streptomyces toxytricini*, was marketed as pancreatic lipase inhibitor (Weibel et al., 1987). It is the only approved anti-obesity drug nowadays. However, some adverse effects on the gastrointestinal system as well as hepatic side effects were reported over long-period consumption (Viner et al., 2010; Filippatos et al., 2008).

Plant contains biologically active phytochemicals or antioxidants that are beneficial in prevention of free-radical induced oxidative stress. Plant-derived phytochemicals may also act as enzyme inhibitor to prevent enzymatic reaction. For example, the presence of lipase inhibitor helps diabetes type 2 patients to control blood glucose and prevent obesity (Alakolanga et al., 2015). Previously, the studies of Jamous et al. (2018) suggested that plant sources which possess with strong antioxidant and pancreatic lipase inhibitory activities, have the potential application in obesity prevention and treatment.

In previous studies, there are some in-vitro and in vivo studies, showed that capsaicin, the component that contributes to the pungent scent of hot chili pepper, is a potential agent for anti-obesity caused by oxidative-stress and adipogenesis of cells. (Leung, 2014; Ritesh et al., 2015) Since this is a quite newly emerging issue, there are only a few shreds of evidence about the effect of capsaicin on anti-obesity properties, therefore the current study is needed to carry out to make further justification on this compound.

Additionally, the antioxidant content and antioxidant activities of local chilies pepper varieties in Malaysia have not been discussed in detail. Therefore, this study was proposed to determine the antioxidant properties in different parts of chili among different local varieties in Malaysia. In the current study, chilies are separated into different parts (seed, pulp, whole fruit) in order to determine their respective antioxidant properties.

1.3 Significance of study

Through this study, the comparison of antioxidant content, antioxidant activities among common local chilies varieties in Malaysia can serve as a reference for the food industry in the future. By using the antioxidant power from natural products, the usage of synthetic antioxidants such as BHA and BHT will be reduced. Thus, the food toxicity and health issues of consumers can be further reduced.

From this study, we can determine the potential of chili seed, which commonly existed as a by-product for both daily consumption and food industry, to contribute significant antioxidant properties as compared to other parts of chilies. At the end of this study, if the antioxidant activities in chilies are comparable with the control of study, it can be suggested as a potential candidate to substitute synthetic antioxidant used in the food industry.

At the same time, this study also determines the potential of selected local chilies varieties, which showed the highest antioxidant activities as an anti-obesity agent besides understanding the mechanism involved through several *in vitro* studies. The results obtained can offer an alternative way of treating obesity using a natural product. Besides, the necessity of adding chilies into the diet of obese patients to supplement the weight loss effect can be determined.

The data of anti-obesity properties among local chilies varieties can be used as a shred of evidence for future nutritional and clinical studies in the issue of obesity. By understanding the possible mechanisms of anti-obesity effect in chili pepper, the weight loss effect in obese patients' diet can be enhanced when chilies are added into it. Thus, by applying such practices, the efficiency of body weight management for overweight or obese patients in Malaysia will be improved in the future with fewer side effects.

1.4 Objectives

General Objective

To determine the antioxidant content, antioxidant activities and anti-obesity properties among different varieties of local chilies (*Cili Pelita*, *Kulai 151*, *Kulai 568*, *Cili Centil* and *Cili Bara*) in Malaysia based on *in-vitro* method.

Specific Objectives

1. To determine and compare antioxidant properties (amount and activities) and capsaicin content in chili varieties (*Cili Pelita*, *Kulai 151*, *Kulai 568*, *Cili Centil* and *Cili Bara*) extracts using *in-vitro* methods.
2. To correlate antioxidant content (total phenolic and total flavonoid content) and antioxidant activities in local chilies varieties using Pearson test.
3. To determine and compare anti-obesity properties of local chilies extracts in 3T3-L1 adipocytes using Oil Red O staining and activity of pancreatic lipase
4. To correlate antioxidant activities and anti-obesity properties in local chili varieties in Malaysia using Pearson test.

1.5 Hypothesis

Alternative Hypothesis

- Objective 1 There is significant different of antioxidant properties (amount and activities) and capsaicin content in chili varieties (*Cili Pelita*, *Kulai 151*, *Kulai 568*, *Cili Centil* and *Cili Bara*) extracts.
- Objective 2 There is significant correlation between antioxidant content (total phenolic and total flavonoid content) with the antioxidant activities in local chilies varieties.
- Objective 3 There is significant different of anti-obesity properties of local chilies extracts in 3T3-L1 adipocytes.
- Objective 4 There is significant correlation between antioxidant activities and anti-obesity properties in local chili varieties in Malaysia.

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