UNIVERSITI PUTRA MALAYSIA

EFFECTS OF MANGOSTEEN (Garcinia mangostana L.) ON BIOCHEMICAL AND MORPHOLOGICAL CHANGES IN LIVER AND KIDNEY OF RATS FED ON HIGH FAT DIET

NORATIRAH SHAZLIN BINTI MUHAMAD ADYAB

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By

NORATIRAH SHAZLIN BINTI MUHAMAD ADYAB

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Master of Science

April 2016

In the name of all mighty Allah SWT,
I would like to dedicate this thesis to my dear parents, Muhamad Adyab Mahadi and Zakiyah Abu Bakar.

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

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Chairman: Professor Asmah Rahmat, PhD
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Obesity is not only worldwide concern as Malaysia also faces increase in the prevalence number of obesity. Obesity always leads to adverse health effect, yet, consumption of vegetables and fruits can prevent it. Nonetheless, a lot of Malaysian is not having enough intakes of vegetables and fruits as recommended. Mangosteen, a purple in colour fruit with fleshy white aril is native fruit from Southeast Asia. Mangosteen contains phenolic compounds named xanthones, anthocyanins and phenolic acids and also a good source of fibre, calcium and phosphorus. The present study addressed the body weight effect, anti-inflammatory and anti-oxidative effects of mangosteen aril in rats feed high fat diet. Forty male Sprague Dawley rats were divided into five groups (n=8), which consisted of normal control group (NC), obese control group (OC), obese supplemented with 200 mg/kg mangosteen group (M200), obese supplemented with 400 mg/kg mangosteen group (M400) and obese supplemented with 600 mg/kg mangosteen group (M600). For 10 weeks, all obese groups were given diet high in fat which contain 414.0 kcal/100g, 43% carbohydrate, 17% protein and 40% fat, while, normal control group were given normal diet with 306.2 kcal/100g, 76% carbohydrate, 21% protein and 3% fat. At the end of ten weeks of diet, alls rats were fasted overnight and 4ml of blood were collected from them. For another seven weeks, obese groups supplemented with mangosteen were force feed to correspond mangosteen dosage while control groups were force feed with distilled water as placebo. At the end of seven weeks supplementation period, all rats were sacrificed before blood, liver and kidney were collected. All data were analyzed using one way ANOVA followed by LSD's multiple range post hoc test. Differences between groups were considered significantly different when p value was less than 0.05. After ten weeks of high fat diet supplementation, all obese group rats had shown significant increment ($p<0.05$) of body weight, with significant lower food intake yet greater in energy intake than normal control group rats. All obese group rats also had higher total cholesterol level, triglyceride level and plasma glucose level than normal control group rats. Besides that, all obese group rats also had lower total antioxidant status (TAS), glutathione peroxidase (GPx) and

superoxide dismutase (SOD) level than normal control group rats. Seven weeks of mangosteen supplementation lead to significant lower ($p<0.05$) of body weight, total cholesterol level, tumor necrosis factor-alpha level (α-TNF) and interleukin-6 level (IL6) of all mangosteen supplementation groups than obese control group. In mangosteen supplementation of M400 and M600 groups, there was significant lower ($p<0.05$) LDL level when compared to obese control group. Other than that, all mangosteen supplementation groups also had significantly higher ($p<0.05$) GPx and TAS level than obese control group. The anti-obesity action of mangosteen aril is possibly via mangosteen bioactive component, xanthones in α-mangostin form. Overall, this study indicates the potential of mangosteen aril as remedies for body weight maintenance, anti-inflammatory an.d anti-oxidative.

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

KESAN MANGGIS (*Garcinia mangostana* L.) TERHADAP PERUBAHAN BIOKIMIA DAN MORFOLOGI HATI DAN BUAH PINGGANG KEATAS TIKUS-TIKUS YANG DIBERI MAKANAN TINGGI LEMAK

Oleh

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Obesiti bukan sahaja menjadi kebimbangan di seluruh dunia, kerana Malaysia juga menghadapi peningkatan jumlah kelaziman obesiti. Obesiti sering memberi kesan buruk kepada kesihatan, namun, pengambilan sayur-sayuran dan buah-buahan mampu mencegahnya. Walau bagaimanapun, kebanyakan rakyat Malaysia tidak mempunyai pengambilan sayur-sayuran dan buah-buahan yang mencukupi seperti yang dicadangkan. Manggis, buah berwarna ungu dengan isi berwarna putih adalah buah yang berasal dari Asia Tenggara. Manggis mempunyai sebatian fenolik bernama xanthone, antosianin dan asid fenolik dan juga sumber yang baik bagi serat, kalsium dan fosforus. Kajian ini merujuk kepada kesan berat badan, anti-radang dan anti-oksidan ke atas isi manggis terhadap tikus-tikus yang diberi makan makanan tinggi lemak. Empat puluh ekor tikus jantan jenis Sprague Dawley telah dibahagi kepada lima kumpulan (n=8), yang mengandungi kumpulan kawalan normal (NC), kumpulan kawalan obes (OC), kumpulan obes yang dibekalkan 200 mg/kg manggis (M200), kumpulan obes yang dibekalkan 400 mg/kg manggis (M400) dan kumpulan obes yang dibekalkan 600 mg/kg manggis (M600). Selama sepuluh minggu, kesemua kumpulan obes telah diberikan makanan tinggi lemak yang mengandungi 414.0 kcal/100g, 43% karbohidrat, 17% protein dan 40% lemak, sementara kumpulan kawalan normal diberikan makanan normal dengan 306.2 kcal/100g, 48.8% karbohidrat, 21% protein dan 3% lemak. Pada penghujung minggu kesepuluh pemberian makanan, semua tikus dipuasakan semalaman dan 4ml darah telah diambil dari mereka. Selama tujuh minggu seterusnya, kumpulan obes yang dibekalkan manggis, diberi secara paksa mengikut dos yang telah ditetapkan, sementara kumpulan kawalan diberi air suling secara paksa sebagai plasebo. Dipenghujung minggu ke tujuh waktu pembekalan, semua tikus akan dikorbankan sebelum darah, hati dan buah pinggang mereka diambil. Semua data dianalisa menggunakan ANOVA satu hala dan diikuti ujian pos hoc julat berganda LSD. Perbezaan antara kumpulan dianggap signifikan apabila nilai p kurang daripada 0.05. Selepas sepuluh minggu pembekalan makanana tinggi lemak, semua tikus dalam kumpulan obes menunjukkan peningkatan siknifikan ($p<0.05$) dalam berat badan,

dengan pengambilan makanan yang siknifikan rendah tetapi tinggi tenaga berbanding tikus dalam kumpulan kawalan normal. Semua tikus dalam kumpulan obes juga mempunyai jumlah kolesterol, jumlah trigliserida dan jumlah gula yang lebih tinggi berbanding tikus dalam kumpulan kawalan normal. Selain itu, semua tikus dalam kumpulan obes juga mempunyai jumlah status antioxidan, jumlah GPx dan jumlah SOD yang lebih rendah berbanding tikus dalam kumpulan kawalan normal. Pembekalan manggis selama tujuh minggu membawa kepada siknifikan yang ledih rendah ($p<0.05$) pada berat badan, jumlah kolesterol, jumlah α-TNF dan jumlah IL6 dalam semua kumpulan obes berbanding kumpulan kawalan obes. Dalam kumpulan M400 dan M600 yang dibekalkan manggis, terdapat siknifikan yang lebih rendah ($p<0.05$) pada jumlah LDL apabila dibandingkan dengan kumpulan kawalan obes. Selain daripada itu, semua kumpulan obes yang dibekalkan manggis juga mempunyai siknifkan yang lebih tinggi ($p<0.05$) pada jumlah GPx dan TAS berbanding kumpulan kawalan obes. Tindak balas anti-obesiti isi manggis mungkin disebabkan oleh komponen bioaktif manggis, xanthones dalam bentuk α-mangostin. Secara keseluruhan, kajian ini menunjukkan potensi isi manggis sebagai agen terhadap pengekalan berat badan, anti-radang dan anti-oxidan.

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This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Master of Science. The members of Supervisory Committee were as follows:

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LIST OF ABBREVIATIONS

α-TNF	alpa-Tumor Necrosis Factor
BMI	Body Mass Index
cm	Centimetre
g	gram
GPx	Glutathione Peroxidase
H&E	Haematoxylin and Eosin
HDL	High Density Lipoprotein
IL-6	Interleukin-6
Kg	Kilogram
LDL	Low Density Lipoprotein
ml	millilitre
mmol/L	millimol per liter
M200	Mangosteen Supplementation at 200 mg/kg
M400	Mangosteen Supplementation at 400 mg/kg
M600	Mangosteen Supplementation at 600 mg/kg
NC	Normal Control
OC	Obese Control
SOD	Superoxide Dismutase
TC	Total Cholesterol
TG	Triglyceride
TAS	Total Antioxidant Status
WHO	World Health Organization
˚C	Degree Celsius
µ	Micro

CHAPTER 1

INTRODUCTION

1.1 Background of Study

Overweight and obesity has become one of new pandemic worldwide nowadays. Statistical data from World Health Organization (WHO) state that overweight and obesity are among fifth leading risk of death in the world (World Health Organization, 2016[1]). Centers for Disease Control and Prevention (CDC) labels overweight and obesity as ranges of weight that are greater than what is generally considered healthy for a given height (Centers for Disease Control and Prevention, 2012). In other terms, overweight and obesity are recognizing as ranges of weight that shown likelihood of certain diseases and health problem.

In order to manage overweight and obesity problem, a lot of methods such as diet modification, exercise, and pharmacotherapy has been introduce. These strategies seem promotable, yet, it is sometime mistreat and overdo (Foster et. al, 2003). Moreover, long term mode, may lead to adverse health effects. For instance, uses of some anti-obesity drugs cause primary pulmonary hypertension, while other cause stimulant action on central nervous system and malabsorption of certain nutrition (World Health Organization, 2000).

Consequently, it is crucial to fabricate overweight and obesity managements that sustain long term efficacy without compromise any side effects. Since before development of modern medicine, natural products derived from plants, animals and mineral sources have been used to treat many diseases. Every part of plants like barks, leaves, hulls, fruits and even the seeds are useful as remedies. The bioactive compound that exist in the plants is belief to have effect on promoting good health (Park, Kim, Park and Yun, 2011; Cherniack, 2008).

Garcinia mangostana or commonly known as mangosteen is native fruits to Southeast Asia. It has high moisture content and a good source of fibre, calcium and phosphorus (Tee et. al, 1997). Some bioactive compound that identified from mangosteen is phenolic compounds named xanthones, anthocyanins and phenolic acid (Naczk et. al, 2011). Of all these, xanthones have been reported as the major phenolics found in mangosteen with apha-mangostin is a major form of the xanthones (Bumrungpert et. al, 2010).

1.2 Problem Statement

Rise of obesity prevalence which doubled since 1980 is clear point that obesity is global challenge. By year 2014, more than 1.9 billion adults, aged 18 years old and older were overweight and obese, while, 42 million children, aged less than five years old were overweight and obese (World Health Organization, 2016[1]). Developed country such as United States and Europe, as well as developing country like Mexico, Thailand and China, also faces obesity as public health concern (Ellulu et. al, 2014; Popkin and Gordon-Larsen, 2004; Caballero, 2007).

Malaysia also is not exclusion as there was increase trend in obesity prevalence. In year 2006, obesity prevalence of adult aged 18-year-old and older was only 14%; however by year 2011, the prevalence had become 15.1% (National Health and Morbidity Survey, 2011). Ultimately, it is predicted that prevalence rate may continue to increase if there is no proper and effective strategies and interventions over this issue (Jan Mohamed et. al, 2015).

Obesity is commonly associated with adverse health problems. Obesity causes abdominal adiposity as well as triggers metabolic function (Moffatt and Stamford, 2006; Hu, 2008). Combination of abdominal adiposity and metabolic disorder is also known as metabolic syndrome. Metabolic syndrome is characterize by central obesity, high triglyceride level, high fasting plasma glucose level, high blood pressure and also low of high density lipoprotein (HDL) level (Katzmarzyk et. al, 2005; Hu, 2008).

Other than that, obesity also triggers free radicals and antioxidants equilibrium (Valko et. al, 2007). Prolong of obesity condition lead to reduction in antioxidant enzyme such as superoxide dismutase (SOD), glutathione peroxidase (GPx) and catalase (CAT) (Molnar, Decsi and Koletzko, 2004; Amirkhizi et. al, 2007). Moreover, obesity also enhance production of inflammatory cytokines such as alpha-Tumor Necrosis Factor (α-TNF), interleukin-6 (IL-6) and interleukin-1β (IL-1β), in which high concentration of inflammatory cytokines is detected in obese individual (Lumeng and Saltiel, 2011; Rodriguez-Hernandez et. al, 2013).

Consequently, association of obesity with metabolic syndrome, reduction in antioxidant enzyme and high accumulation of inflammatory cytokines, cause greater risk for adverse health conditions like atherosclerosis, cardiovascular diseases, diabetes mellitus and cancer (Hu, 2008; Moffatt and Stamford, 2006; Rodriguez-Hernandez et. al, 2013).

1.3 Significant of Study

Malaysian Dietary Guidelines recommended intake of five serving vegetables and fruits daily (Ministry of Health, 2010). The basis of recommendations is the facts that vegetables and fruits are nutritious through beneficial combinations of micronutrients, antioxidants and phytochemicals (Agundo, 2005; Liu et. al, 2000). Other features like high water content, high in dietary fibre, as well as relatively low energy density, enhance these food profiles (Tetens and Alinia, 2009).

Adequate intake of vegetables and fruits is favourable in prevention of obesity and reducing risk of cardiovascular diseases (Tentens and Alinia, 2009; Liu et. al, 2000). Foods which in high dietary fibre content may boost postprandial satiety while adding palatability to diet, hence, lessen subsequent hunger (Howarth et. al, 2001; McCrory et. al, 2000). Subsequently, high dietary diet intake in long term, possibly lead to decline in energy intake, as well as body weight (Tentens and Alinia, 2009).

Despite the beneficial role of vegetables and fruits toward health, yet, 92.5% of Malaysian adult, aged 18 years old and over still consumed less than recommended by Malaysia Dietary Guidelines (NHMS, 2011). Therefore, encouragement on important of vegetables and fruits towards wellness should be emphasized.

Mangosteen, dark purple fruit with white flesh aril is delicious fruits with abundant of xanthones (Bumrungpert et. al, 2010). All component of mangosteen fruit, outer pericarp, inner pericarp, aril and seed has varies amount of antioxidants (Chaovanalikit et. al, 2012; Gutierrez-Orozco and Failla, 2013). Interest over antioxidants mangosteen pericarp has lead to a lot of litureture of mangosteen pericarp on anti inflammatory, anti cancer, antioxidant and anti bacterial (Sampath and Vijayaraghavan, 2007; Chomnawang et. al, 2007; Adiputro et al, 2013, Jindarat, 2014). Meanwhile, mangosteen aril potential in antioxidant, anti inflammation is unknown. Hence, this study is address to evaluate the potential of mangosteen aril.

1.4 General objective

To investigate effects of mangosteen aril on high fat diet induced rats

1.5 Specific Objective

i. To determine and compare body weight between normal control, obese control and mangosteen supplementation group.

ii. To determine and compare biochemical profile (glucose, total cholesterol, triglyceride, HDL-cholesterol and LDL-cholesterol) between normal control, obese control and mangosteen supplementation group.
iii. To determine and compare antioxidant enzyme profile (total antioxidant status, glutathione peroxidase and superoxide dismutase) between normal control, obese control and mangosteen supplementation group.
iv. To determine and compare inflammatory biomarkers (α-TNF and IL-6) between normal control, obese control and mangosteen supplementation group.
v. To determine and compare liver and kidney histology between normal control, obese control and mangosteen supplementation group.

1.6 Hypothesis

i. Mangosteen supplementation group have lower body weight than obese control group.
ii. Mangosteen supplementation group have lower glucose, total cholesterol, triglyceride, LDL-cholesterol, α-TNF and IL-6 level than obese control group.
iii. Mangosteen supplementation group have higher HDL-cholesterol, total antioxidant status, glutathione peroxidase and superoxide dismutase level than obese control group.
iv. Mangosteen supplementation group have similar liver and kidney histology finding with normal control group.

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