

IN VITRO LIPID ACTIVITY OF *Eurycoma longifolia* JACK EXTRACTS  
LOADED LIPOSOME

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A thesis submitted in fulfillment of  
the requirements for the award of the degree of  
Master of Engineering (Bioprocess)

Faculty of Chemical Engineering  
Universiti Teknologi Malaysia

MAY 2014

To my Mom and Dad who always love me unconditionally.

To Dr Harisun Yaakob who always believe in me.

## ACKNOWLEDGEMENTS

Praise to the Allah, the creator of this world. Firstly, I would like to thank my mom and dad who always love me unconditionally, who always been there no matter in any situation whether I am in my happiest days or my gloomy days. Furthermore, I would like to thank both them for always being my number one supporter, motivator, adviser and my inspiration for me to complete this project and lead my life. I would also like to thank them for always support me in my passion in research and unconditionally support me during my financial instability. I will always love you mom and dad.

Secondly, I would like to thank my supervisor, Dr Harisun Yaakob who always believed in me in no matter situations. Furthermore, I would to thank her for all the guidance given to me especially in this project and guidance given for me to lead my life as a better person. I also would like to thank her for all the support she had given to me, the motivation and encouragement which help me to complete this project. Thank you Dr.

Thirdly, I would like to thank my friend and colleagues who had helped me to complete this project. I would like to thank to Mukrish, Ain, Roza, Afiq, Nabil, Hafizi, Wan Najihah, Ardawati, Liza, Wan Azrin. Thank you very much and make me becoming a better person.

## ABSTRACT

*Eurycoma longifolia* Jack (ELJ) is an alternative medicine that could be used to treat obesity problem due to testosterone hormone enhancer capabilities, which enable enhancement of carbohydrate, fat and protein metabolism. However, its effect is slower than synthetic drug, because of low bioavailability problem. Liposome could be used as vehicle to enhance bioavailability. Cytotoxicity study was conducted and 100  $\mu\text{g/ml}$  of ELJ extract was determined as safe dosage for 3T3-L1 preadipocyte cells. Exposure of the ELJ extracts (100  $\mu\text{g/ml}$ ) on adipocyte cells for 5 hours showed the highest Free Fatty Acid (FFA) release similar to positive control with no significant different ( $p>0.05$ ). Formulation of ELJ loaded liposome was optimized using Central Composite Design (CCD) of Response Surface Methodology (RSM). Lecithin (LC) and cholesterol (CH) were the independent variables and  $\zeta$ -potential and encapsulation efficiency (EE) of ELJ extracts were the dependent variables. Production of liposome caused  $\zeta$ -potential to become more negative, after LC concentration was increased from 1.41% to 2.59%, while CH did not give much effect. Furthermore, concentrations of LC and CH at 2.0% and 0.6% depicted optimum EE. Optimization producing a  $\zeta$ -potential value of -58.5 mV and EE of 55.0% when LC and CH concentration at 1.97% (w/v) and 0.61% (w/v) respectively. Independent experiment validated the optimization by identifying the mean of differences and standard error between the predicted and actual data at 4.39 mV and 3.42 for  $\zeta$ -potential and 6.57% and 5.00 for EE respectively which had not significant different ( $p>0.05$ ) from predicted value. ELJ loaded liposome exposed to adipocyte cells showed highest increment by 1.5 fold more FFA release compared to ELJ extracts at concentration 10  $\mu\text{g/ml}$  at 5 hours of incubation. Time dependent analysis using 10  $\mu\text{g/ml}$  ELJ loaded liposome identified 4 hours as the optimum incubation time generated 122.83  $\mu\text{M}$  FFA release, 1.22 fold more than ELJ extract. From this study, it could be suggested that encapsulation of ELJ extracts in liposome may increase the lipolysis of fat and bioavailability in human.

## ABSTRAK

*Eurycoma longifolia* Jack (ELJ) adalah salah satu ubat alternatif yang boleh digunakan untuk mengatasi masalah obesiti kerana mampu meningkatkan kadar hormon testosteron dan testosteron mempunyai potensi untuk meningkatkan metabolisme karbohidrat, lemak dan protein. Akan tetapi, kesan ELJ ekstrak adalah lebih lambat berbanding ubat sintetik kerana masalah bioperolehannya yang rendah. Liposom boleh digunakan sebagai cara meningkatkan bioperolehan tersebut. Kajian kesitotoksian telah dijalankan dan 100 µg/ml adalah dos yang selamat untuk sel 3T3-L1 preadiposit. Pendedahan ekstrak ELJ (100 µg/ml) ke atas sel adiposit selama 5 jam menunjukkan pembebasan Asid Lemak Bebas (FFA) tertinggi menyerupai kawalan positif dengan tiada perbezaan ketara ( $p > 0.05$ ). Kaedah Reka Bentuk Komposit Berpusat (CCD) daripada Kaedah Tindak Balas Permukaan (RSM) telah digunakan untuk mengoptimumkan formulasi penyediaan ELJ di dalam liposome. Lesitin (LC) dan kolesterol (CH) adalah pembolehubah bebas, manakala potensi- $\zeta$  dan kecekapan pengkapsulan (EE) adalah pembolehubah bersandar. Penghasilan liposom menyebabkan potensi- $\zeta$  menjadi lebih negatif, selepas kepekatan LC meningkat daripada 1.4% kepada 2.59%, manakala CH tidak memberi kesan yang besar. Sehubungan itu, kepekatan LC dan CH adalah pada 2.0% dan 0.6% menunjukkan EE yang optimum. Optimisasi menghasilkan nilai potensi- $\zeta$  pada -58.5 mV dan EE pada 55.0% apabila kepekatan LC dan CH berada pada 1.97% (w/v) dan 0.61 (w/v). Ekperimen bebas mengesahkan hasil daripada optimisasi di mana perbezaan min dan ralat piawai di antara nilai ramalan dan nilai sebenar adalah 4.39 mV dan 3.42 untuk potensi- $\zeta$ , manakala 6.57% dan 5.00 untuk EE tanpa perbezaan ketara ( $p > 0.05$ ) dengan nilai ramalan. Pendedahan liposom mengandungi ELJ kepada sel adiposit menunjukkan kenaikan tertinggi sebanyak 1.5 kali ganda pembebasan FFA melebihi ekstrak ELJ pada kepekatan 10 µg/ml dalam tempoh 5 jam inkubasi. Analisis bersandarkan masa menunjukkan 4 jam sebagai masa yang optimum untuk inkubasi, menghasilkan 122.83 µM pembebasan FFA, 1.22 kali ganda melebihi ekstrak ELJ. Berdasarkan kajian ini, boleh dicadangkan pengkapsulan ekstrak ELJ di dalam liposom dapat meningkatkan aktiviti lipolisis lemak dan bioperolehan di dalam badan manusia.

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## LIST OF ABBREVIATIONS

ANOVA	-	Analysis of variance
ATGL	-	Adipose Triglyceride Lipase
ATP	-	Adenosine Triphosphate
BMI	-	Body Mass Index
cAMP	-	Cyclic Adenosine Monophosphate
CBS	-	Calf Bovine Serum
CCD	-	Central Composite Design
CH	-	Cholesterol
CO <sub>2</sub>	-	Carbon Dioxide
DAG	-	Diacylglycerol
DLS	-	Dynamic Light Scattering
DMEM	-	Dulbecco Modified Eagle Medium
DMSO	-	Dimethyl sulfoxide
DVLO	-	Derjaguin, Verwey, Landau, Overbeek
EE	-	Encapsulation Efficiency
ELJ	-	<i>Eurycoma longifolia</i> Jack
FDA	-	Food and Drug Administration
FFA	-	Free Fatty Acid
HDL	-	High Density Lipoprotein
HPLC	-	High Performance Liquid Chromatography
HSL	-	Hormone sensitive lipase
IC <sub>50</sub>	-	Inhibitory Concentration 50 %
IgE	-	Immunoglobulin E

LDL	-	Low Density Lipoprotein
MAG	-	Monoacylglycerol
MGL	-	Monoglyceride Lipase
MLV	-	Multilamellar vesicle
MTT	-	3-[4, 5-dimethyl-thiazol-2-yl]-2, 5-diphenyl tetrazolium bromide
OH	-	Hydroxyl group
PBS	-	Phosphate Buffer Saline
Pen-Strep	-	Penicillin and Streptomycin
Peri A	-	Perilipin A
PC	-	Phosphatidylcholine
PKA	-	Protein Kinase A
PL	-	Phospholipids
psi	-	Pound-force per Square Inch
Rpm	-	Rotation Over Minute
SPC/SDC	-	Mixture of Soy Bean Phosphatidylcholine and Sodium Deoxycholate
SUV	-	Small Unilamellar Vesicle
TAG	-	Triacylglyceride

## LIST OF SYMBOLS

%	-	Percentage
°	-	Degree
°C	-	Degree Celsius
$\kappa^{-1}$	-	Debye length
ζ- Potential	-	Zeta Potential
μg/ml	-	Micro gram over milliliter
μl	-	Microliter
μM	-	MicroMolar
μm	-	Micrometer
Cells/ml	-	Cells over Milliliter
Cells/well	-	Cells over Well
G	-	Gravity Constant
g	-	Gram
Hz	-	Hertz
hr	-	Hour
kg/m <sup>2</sup>	-	Kilogram over Metre Square
KOH	-	Potassium Hydroxide
M	-	Molar
mg/kg	-	Milligram over Kilogram
mg kg BW <sup>-1</sup>	-	Milligram Kilogram per Body Weight
mM	-	Millimolar
ml	-	Milliliter
min	-	Minute
mV	-	Milivolt
N	-	Normality



nm	-	Nanometer
OD	-	Optical Density
$p > 0.05$	-	Significant value more than 95%
$p < 0.05$	-	Significant value less than 95%
$V_A$	-	Sum of Van der Waals Attractive
$V_R$	-	Electrical Double Layer Repulsion
$V_S$	-	Potential Energy due to Solvent
$V_T$	-	Total Potential Energy Function
v/v	-	Volume over Volume
w/v	-	Weight over Volume

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## **CHAPTER 1**

### **INTRODUCTION**

#### **1.1 Introduction**

Since 1980, obesity problem had risen to endemic proportions (Mathew *et al.*, 2008). Khor (2012) had reported, more than 78 millions adults and 12.5 million children and adolescents were obese in 2009-2010 in United States. The number of obese in Malaysia also escalating to three folds from 4.4% to 14% over the period of 10 years as reported by the second and third National Health and Morbidity Surveys in 1996 and 2006 (Khor, 2012). Obesity was classified when a person has Body Mass Index (BMI) more than 30 (Mathew *et al.*, 2008). However this figure may be inaccurate, since Asian BMI was lower than BMI from Europe and United States. This was proven by the increases of cardiovascular disease from people which has lower BMI from obese BMI (Zaher *et al.*, 2009).

The increasing number of obesity through out the world, had caused more people suffered from various types of diseases. For example, obese people can develop insulin resistance inside the body, since the pancreas cannot cope with overload of glucose in the blood. Thus, they prone to get diseases like diabetic

dyslipidemia, hypertension and type 2 diabetes melitus (Greenfield and Campbell, 2004).

Obesity is an expensive disease. Obese people need to buy various types of medicines. They need to buy medicine for diabetic, hypertension, and worst for cardiovascular diseases. Irony, the price of each of the medicine was becoming more expensive as year go on. In 2005, it was estimated the expenditure for medicine by Malaysian was worth RM2.24 billion (Sameerah and Sarojini, 2005). Malaysian had spent millions of ringgit for drugs for hypertension medicine (Amlodipine, RM 69.8 million), controlling cholesterol (Simvastatin, RM 67.2 million) and diabetic medicine (RM 91.5 million) (Sameerah and Sarojini, 2005). All the medicine prescribed above can be interrelated because of obesity.

Currently, obesity is treated with drug like Orlistat, where it works by inhibit the gastric, pancreatic and carboxylester lipase (Gooda *et al.*, 2012). Consumption of Orlistat orally three times a day at concentration 120 mg able to block 30% of dietary fat adsorption due to inhibition of gastrointestinal lipase (Gooda *et al.*, 2012). Furthermore, obesity also could be treated by appetite suppression, modulation of adipocytes proliferation and differentiation, the adipogenic factors, increase in thermogenesis or inhibition of fatty acid synthases (FAS) (Gooda *et al.*, 2012). Interesting to note, consumption of drug for weight lost was only approved to be consumed for two years only by Food and Drug Administration (FDA), thus, with short period of time, the drug fail to deliver the effect desired and the consumer exposed to side effect from the drug (Gooda *et al.*, 2012). Natural based product to remedy obesity is gained more popularity nowadays, since many people are worried with the side effect caused by the synthetic drug, therefore, many research have been conducted to incorporate modern technique with natural products and improved the efficacy of the natural product toward the target area. For example, Kim, Hyun, and Choung (2006) had reported, cinnamon able to reduce glucose level in blood, increase serum insulin, decrease triglyceride and increase HDL-cholesterol. Furthermore, consuming the plant extract was found to be beneficial to obese patient since it helped to improve the glucose metabolism, lipid metabolism, antioxidant and

capillary function (Khan *et al.*, 2003). It was identified, *Rubi fructus* fruit, *Corni fructus* fruit, *Salicis radices cortex* bark and *Geranium nepalense* shown to have anti-obesity agents which inhibit lipid formation in 3T3-L1 adipocytes (Roh and Jung, 2012).

*Eurycoma longifolia* Jack, ELJ (Tongkat Ali) is well known for an aphrodisiac plant. Apart from that, it had been used traditionally for curing malaria, pyretic, and ulcer cytotoxic (Bhat and Karim, 2010). Studies had found, administration of ELJ extracts on male rats had increased the libido activities and testosterone level in male rat (Bhat and Karim, 2010). Furthermore, it had been found, ELJ extracts administrated to rat can reduce hyperglycemic effect (Husen, Pihie, and Nallappan, 2004). Thus, this report suggesting lipogenesis could be reduced and deposition of fat will be lowered. As a result, the amount of weight can be reduced.

## 1.2 Problem Statement

ELJ extract is a good alternative that could be used to treat the obesity problem. This is due to the ability of ELJ that can increase testosterone hormone level in the body (Tambi and Imran, 2010), due to testosterone is important for metabolism of carbohydrate, fat and protein. Low amount of testosterone influence on body fat composition and muscle mass in male affecting fat mass increased, decreased of insulin sensitivity, glucose tolerance impaired and spiked of triglycerides and cholesterol and low high density lipid-cholesterol (Kelly and Jones, 2013) . However, the effect of the ELJ extract is slower than the synthetic drug. This is due to most of phytochemical like eurycomanone in ELJ extract has a poor bioavailability owing to its poor membrane permeability which mentioned by Low *et al.* (2005) had found that eurycomanone in the blood plasma concentration of rats was five-fold lower when administrated orally compared to intravenous administration, even though the concentration of eurycomanone used in oral

administration was five times higher than in intravenous method. Therefore, a carrier or vehicle can be used to increase the efficacies of the ELJ extract to treat the obesity problem.

Bioavailability of the phytochemical in ELJ can be enhanced by encapsulate the phytochemical into a lipid carriers like liposome, solid lipid nano-particles, oily suspensions, submicron lipid emulsion, lipid implants, lipid microtubules, lipid micro bubbles and lipid microsphere (Rawat *et al.*, 2008). Each of the lipid carriers mentioned has their own advantages and disadvantages, which made liposome, was being chosen to encapsulate the ELJ extracts due to size range, composition, features and common preparation techniques. Many studies has proven that liposome as a carrier can increase the effect of the drugs like treatment of acne using tretinoin, treatment of atopic eczema using glucocorticoids, as an anaesthetic using lignocaine and tetracaine (Badran, Shalaby, and Al-Omrani, 2012) and inhibit the grow of breast tumour using paclitaxel (Yang *et al.*, 2007). Encapsulation of ELJ extracts within liposomes is hope that it can increase the bioavailability, thus facilitate adsorption of ELJ through the plasma membrane and ultimately the bioactive are delivered to the targeted site. The properties of liposomes are similar to those of lipoprotein phospholipids monolayer. Therefore liposomes are recognised at the cell membrane for lipid transfer (Podlipec, 2010).

This study is expected to result in novel insight of understanding the role of ELJ extract on lipid metabolism that can prevent metabolite diseases like obesity. Furthermore the effective delivery system that able to facilitate its effectiveness can be obtained and provide the improvement of the delivery of plant extract for nutraceutical application.

### 1.3 Hypothesis

Lipolysis can be enhanced by using liposome coated with ELJ extract compared with ELJ extracts alone.

### 1.4 Objective

The objectives of this study were to develop and optimize the ELJ extract loaded liposome formulation for lipid digestion activity enhancement

### 1.5 Scope

- i. Identification of lipolysis effect when ELJ exposed to lipid via cell cultures analysis.
- ii. Formulation of the optimum formulation and characterise the ELJ extract into liposome.
- iii. Determination of the effect of ELJ loaded liposome towards *in-vitro* lipolysis.

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