UNIVERSITI PUTRA MALAYSIA

IDENTIFICATION OF LIPASE INHIBITOR FROM Orthosiphon stamineus Benth AND ANALYSIS OF LIPASE-INHIBITOR COMPLEX INTERACTION

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By

NORSYUHADA ALIAS

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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

June 2016

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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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NORSYUHADA ALIAS

June 2016

Chairman : Prof. Raja Noor Zaliha Raja Abd. Rahman, D. Eng
Faculty : Biotechnology and Biomolecular Sciences

Natural products are a vast source of potential compounds that can be developed as an anti-obesity agent. One of the mechanisms of anti-obesity agents is inhibition of pancreatic lipase. Orlistat is the only commercial pancreatic lipase inhibitor with FDA approval, but it is derived synthetically and has side effects. Hence, there is a need to find for alternative from natural resources. It is postulated that lipase inhibitor from local plants could change pancreatic lipase structure conformation and impair it function. Therefore, this study aims to screen selected plants for pancreatic lipase-inhibitory activity, to identify the lipase-inhibitory compound and to analyse the lipase-inhibitor complex interaction. Screening of 24 crude extracts for their *in vitro* activity against porcine pancreatic lipase (PPL) detected four extracts demonstrating high (>70%) inhibition, while seven extracts had medium (30-70%) inhibition and the remaining 13 extracts exhibited low (<30%) inhibition when incubated with PPL at a final concentration of 500 µg/ml for 10 min at 37°C. *P. niruri* extract displayed the most potent PPL inhibitor, followed by *O. stamineus*, *M. paniculata* and *A. bilimbi* with the IC_{50} value of 27.7<34.7<41.5<55.2 µg/ml, respectively. The best two extracts, namely *P. niruri* and *O. stamineus,* showed noncompetitive and uncompetitive inhibition, respectively. *P. niruri* and *O. stamineus* showed total phenolic content of 431.0 ± 0.01 and 103.0 ± 0.01 mg GAE/g dry extract, while total flavonoid content of 14.8 ± 0.07 and 21.6 ± 0.03 mg QE/g dry extract, respectively. Both *P. niruri* and *O. stamineus* extracts showed high antioxidant activity, with EC_{50} values of 8.4 and 26.3 µg/ml, respectively. Isolation of lipase-inhibitory compound from *P. niruri* and *O. stamineus* was performed via chromatographic approaches. However, the isolation process later came to focus on *O. stamineus* active fractions due to difficulty separating the *P. niruri* active fraction. A combined fraction of MK38 and MK39 from *O. stamineus* extract demonstrated the highest inhibitory activity with 50% PPL inhibition. Fractionation of combined fraction MK38 and MK39 by high-performance liquid chromatography (HPLC) yielded an active compound designated as sub-fraction P5 with 45% PPL inhibition. Sub-fraction

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P5 was authenticated as rosmarinic acid by spectroscopic analyses, namely liquid chromatography-mass spectrometry-mass spectrometry (MS-MS), Fourier transform infrared spectroscopy (FTIR), and nuclear magnetic resonance (NMR). Rosmarinic acid inhibited PPL in a non-competitive manner with an IC_{50} value of 19.5 µg/ml. Circular dichroism analysis showed a conformational change of the PPL secondary structure upon binding of rosmarinic acid towards PPL. However, no diffraction data were acquired from X-ray crystallography technique. Molecular docking predicted the potential binding site of rosmarinic acid was positioned far from the active site, whereas a molecular dynamic simulation projected that the flexibility of PPL structure would be affected upon binding of rosmarinic acid towards PPL. Hence, the *In silico* results were in agreement with the inhibition mode analysis. These results have suggested that rosmarinic acid from *O. stamineus* may play a complimentary role in obesity treatment, acting as a non-competitive pancreatic lipase inhibitor.

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

PENGENALPASTIAN PERENCAT LIPASE DARI *Orthosiphon stamineus* Benth DAN ANALISIS TERHADAP INTERAKSI DI ANTARA KOMPLEKS LIPASE – PERENCAT

Oleh

NORSYUHADA ALIAS

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Pengerusi : Prof. Raja Noor Zaliha Raja Abd. Rahman, D. Eng
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Tumbuhan dari sumber semula jadi berpotensi untuk menghasilkan agen anti-obesiti. Salah satu mekanisme agen anti-obesiti adalah dengan merencat aktiviti lipase dari pankreas. Orlistat adalah satu-satunya perencat lipase komersial yang mendapat kelulusan FDA, tetapi ianya dihasilkan secara sintetik dan mempunyai kesan sampingan. Justeru, ada keperluan untuk mendapatkan alternatif dari sumber semulajadi. Adalah dijangkakan yang lipase perencat dari tumbuhan tempatan boleh mengubah konformasi struktur lipase dari pankreas dan menjejaskan fungsinya. Jadi, penyelidikan ini bertujuan untuk menyaring tumbuhan terpilih yang mampu merencat aktiviti lipase dari pankreas, untuk mengenalpasti sebatian perencat lipase dan untuk menganalisa interaksi di antara kompleks lipase-perencat. Saringan 24 ekstrak dari tumbuhan terpilih yang berpotensi merencat aktiviti lipase dari pankreas khinzir (PPL) secara *in vitro* mendapati empat ekstrak menunjukkan perencatan tertinggi (>70% perencatan), tujuh ekstrak menunjukkan perencatan sederhana (30–70% perencatan) dan 13 ekstrak menunjukkan perencatan yang rendah (<30% perencatan) terhadap aktiviti lipase apabila diasai dengan PPL pada kepekatan akhir sebanyak 500 µg/ml selama 10 minit pada suhu 37°C. Ektrak dari *P. niruri* adalah perencat yang paling berkesan, diikuti oleh ekstrak dari *O. stamineus*, *M. paniculata* dan *A. bilimbi* dengan masing-masing menunjukkan nilai IC_{50} sebanyak 27.7<34.7<41.5<55.2 µg/ml. Dua ekstrak terbaik, iaitu *P. niruri* dan *O. stamineus*, masing-masing merencat PPL secara non-kompetitif dan un-kompetitif. *P. niruri* dan *O. stamineus*, masing-masing menunjukkan kandungan fenolik berjumlah 431.0 ± 0.01 dan 103.0 ± 0.01 mg GAE/g ekstrak kering manakala kandungan flavonoid berjumlah 14.8 ± 0.07 dan 21.6 ± 0.03 mg QE/g ekstrak kering. Kedua-dua ekstrak *P. niruri* dan *O. stamineus* menunjukkan aktiviti antioksidan yang tinggi dengan nilai EC_{50} masing-masing sebanyak 8.4 dan 26.3 µg/ml. Proses pengasingan sebatian dari kedua-dua ekstrak *O. stamineus* dan *P. niruri* telah dibuat dengan menggunakan kaedah kromatografi. Walau bagaimanapun,

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proses pengasingan sebatian kemudiannya hanya tertumpu kepada pecahan aktif *O. stamineus* kerana kesukaran memisahkan pecahan aktif dari ekstrak *P. niruri*. Gabungan pecahan MK38 dan MK39 daripada ekstrak *O. stamineus* menunjukkan aktiviti perencatan tertinggi dengan 50% aktiviti lipase berjaya direncat. Pemeringkatan kedua-dua pecahan menggunakan kromatografi cecair berprestasi tinggi (HPLC) berjaya memperolehi sebatian aktif yang dinamakan sebagai sub-pecahan P5 yang merencatkan aktiviti PPL sebanyak 45%. Sub-pecahan P5 telah disahkan sebagai asid rosmarinik melalui beberapa analisis spektroskopi iaitu kromatografi cecair gandingan spektrometri jisim-spektrometri jisim (MS-MS), spektroskopi inframerah transformasi Fourier (FTIR) dan spektrometer resonans magnet nukleus (NMR). Asid rosmarinik merencat aktiviti PPL secara non-kompetitif dengan nilai IC_{50} sebanyak 19.5 µg/ml. Analisis 'circular dichroism' pula menunjukkan berlakunya perubahan konformasi di dalam struktur PPL apabila ia bergabung dengan asid rosmarinik. Walaupun begitu, tiada sebarang data pembelauan diperolehi daripada teknik kristalografi sinar-X. Dok molekul menjangkakan asid rosmarinik mengikat struktur PPL pada kedudukan yang jauh dari tapak aktif manakala simulasi molekul dinamik menunjukkan bahawa fleksibiliti struktur PPL terjejas apabila berlakunya interaksi dengan asid rosmarinik. Oleh itu, hasil kajian *In silico* adalah selari dengan analisis mod perencatan. Kesimpulannya, asid rosmarinik dari *O. stamineus* boleh memainkan peranan bagi merawat kegemukan di mana ia bertindak sebagai perencat lipase dari pankreas secara non-kompetitif.

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I certify that a Thesis Examination Committee has met on 13 June 2016 to conduct the final examination of Norsyuhada bt Alias on her thesis entitled "Identification of Lipase Inhibitor from *Orthosiphon stamineus* Benth and Analysis of Lipase-Inhibitor Complex Interaction" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the Doctor of Philosophy.

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LIST OF ABBREVIATIONS

Å	Angstrom
CLP	Porcine colipase
Da	Dalton
ºC	Degree Celsius
EDTA	Ethylenediaminetetraacetic acid
FDA	Food and Drug Administration
FTIR	Fourier transform infrared spectroscopy
HDL	High-density lipoprotein
HPL	Human pancreatic lipase
HPLC	High performance liquid chromatography
KBr	Potassium bromide
kDa	Kilodalton
LC-MS	Liquid chromatography-mass spectrometry
LPL	Lipoprotein lipase
M	Molar
mA	Milliampere
mg	Milligram
min	Minute
ml	Milliliter
mM	Milimolar
MS-MS	Liquid chromatography-mass spectrometry-mass spectrometry
MWCO	Molecular weight cut off
nm	Nanometer
NMR	Nuclear magnetic resonance
OD	Optical density
pNPB	*p*-nitrophenyl butyrate
PPL	Porcine pancreatic lipase
PL	Pancreatic lipase
RA	Rosmarinic acid
SDS-PAGE	Sodium dodecyl sulphate polyacrylamide gel electrophoresis
SDS	Sodium dodecyl sulphate
STZ	Streptozotocin
TEMED	N, N, N, N-Tetramethylenediamide
TLC	Thin-layer chromatography
U	Unit of activity
U/mg	Unit per milligram
U/ml	Unit per milliliter
UV	Ultraviolet
V	Volt
v/v	Volume per volume
w/v	Weight per volume
µg	Microgram
µl	Microliter
µm	Micrometer

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CHAPTER 1

INTRODUCTION

Obesity has been classified as an epidemic affecting both developed and developing countries worldwide. The prevalence of obesity at an alarming rate has led to a rise of medical costs. More importantly, concerns about obesity are not about 'looking good' and having a beautiful silhouette, but merely maintaining a disease-free and healthy body. Obesity is known to facilitate the development of chronic diseases such as type 2 diabetes mellitus, hypertension, heart attack, stroke, osteoarthritis, sleep apnea, and some type of cancers (Mohamed *et al*., 2014; Wan Mohamud *et al*., 2011). The rise of these obesity-associated complications has compelled researchers to seek out lasting solutions for weight management and control. Although reduction of caloric intake by diet and increased level of physical activity are the most recommended approaches to lose weight, these attempts do not always work. Basically, suitable weight-loss programs depend on obesity level, overall health, and the patient's inclination to take part in the weight-loss plan. The treatment tools include dietary modifications, exercise, behaviour change, prescription of weight-loss medications and weight-loss surgery as the last resort (Glazer, 2001).

1.1 Problem statement

Nowadays, the need for anti-obesity drugs and other supplements is fast gaining recognition. There are many anti-obesity drugs in the market that have received approval from the U.S Food and Drug Administration (FDA). These anti-obesity drugs have specific mode of action to treat obesity. However, practically all of them have side effects. This was proven with the withdrawal of sibutramine, rimonabant, and a few other anti-obesity drugs from the European market due to their adverse side effects. The most effective lipase inhibitor in the market right now is orlistat. Orlistat is an over-the counter medication that is also labeled as a fat blocker. However, orlistat is a synthetic drug with side effects. Orlistat may cause severe liver and kidney problems (Filippatos *et al*., 2008). It also inhibits the absorption of certain vitamins in the body. This indicates a need to find an effective and safe lipase inhibitor. Currently, most of the commercial non-prescribed slimming preparations available in the market are derived from plants. Various side effects from the synthetic drug application have prompted interest in the use of medication derived from natural sources. This indicates that plant-based materials may be an interesting sources for the development of anti-obesity agents, especially the one targeting on pancreatic lipase inhibition.

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1.2 Rationale and novelty of the study

Malaysia is a tropical country rich with plants and herbs which are yet to be explored for their benefits. Many plants have traditionally been used as slimming aids by various communities in Malaysia, for daily consumptions or external used such as ointments and creams. Although the use of plant-based materials to lose weight has been based on the knowledge handed down through generations, their scientific evidence is still lacking and not well documented. There has been no detailed study of compound(s) contributing to the lipase inhibition action or anti-obesity property of these prospective plants. Hence, this study is vital to reveal the potential ability of selected plants in Malaysia as anti-obesity agents. This study would identify local plant(s) with the lipase-inhibition action and uncover the mechanisms through which the lipase-inhibitory compound acts. This could strengthen the fundamental knowledge on the interaction between lipase and its inhibitor. Various approaches have been applied in drug-discovery technology in order to develop new drugs. In this study, a combination of computer technology with the existing instrumentation, such as X-ray crystallography and circular dichroism, was chosen to study protein-ligand interaction. This provides exposure to high-end technology and diversifies the utilization of these sophisticated instruments provided by the university.

1.3 Hypothesis

Local plants selected in this study have a potential compound(s) capable of inhibiting pancreatic lipase. Binding interaction of the inhibitory compound(s) towards pancreatic lipase could trigger conformational changes of the pancreatic lipase structure that might impair its function.

1.4 Objectives of the project

This thesis aims to gain an understanding of the mechanism of pancreatic lipase inhibition of prospective Malaysian plants. The general aim results in several objectives:

1. Screening of selected plants for pancreatic lipase-inhibitory activity.
2. Isolation and identification of a pancreatic lipase-inhibitory compound.
3. Analysis of the pancreatic lipase-inhibitor complex interaction.

1.5 Outline of the thesis

Plants and herbs are natural sources of pancreatic lipase inhibitor for obesity treatment. A review of the prevalence of obesity, natural products as a potential source of anti-obesity agent, and the technology available to study the lipase inhibition action is contained in Chapter 2. Screening of selected Malaysian plants was performed to identify the potential plant(s) with the highest inhibition activity against pancreatic lipase and related in Chapter 3. Isolation of the

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active compound was carried out by several chromatographic techniques, while the identification of the active compound was performed using several spectroscopic methods, as described in Chapter 4. Chapter 5 contains analyses of the protein-ligand complex interaction between the pancreatic lipase and the active compound (the potential lipase inhibitor), conducted by incorporating experimental testing with a computational approach. Finally, a summary of the results obtained in this thesis and recommendations for future study is contained in Chapter 6.

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