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CHARACTERIZATION OF DPP-4 and α-AMYLASE INHIBITORS FROM Melicope glabra (Blume) T.G.Hartley AND Melicope latifolia (DC.) T.G.Hartley (RUTACEAE) FOR TYPE 2 DIABETES THERAPY

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By

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CHARACTERIZATION OF DPP-4 and α-AMYLASE INHIBITORS FROM *Melicope glabra* (Blume) T.G.Hartley AND *Melicope latifolia* (DC.) T.G.Hartley (RUTACEAE) FOR TYPE 2 DIABETES THERAPY

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Chairman : Nur Kartinee Binti Kassim, PhD
Faculty : Science

Melicope glabra and *Melicope latifolia* are plants of Rutaceae family that can be found locally in Malaysia. To date, scientific reports on the phytochemicals and bioactivities of the two species are still limited, especially on antidiabetic activity. In this research, the potential antidiabetic properties and bioactive components of *M. glabra* and *M. latifolia* were investigated. Assay-guided isolation of phytoconstituents on *M. glabra* gave five compounds which were *p*-geranyl coumaric acid (**49**), stigmasterol (**56**), scopoletin (**64**), evolitrine (**12**), and pachypodol (**68**). Notably, *p*-geranyl coumaric acid (**49**) and evolitrine (**12**) were isolated for the first time from the species *M. glabra*. Meanwhile, four compounds were isolated from *M. latifolia* namely β-sitosterol (**55**), halfordin (**88**), methyl *p*-coumarate (**89**), and protocatechuic acid (**90**). Halfordin (**88**), methyl *p*-coumarate (**89**), and protocatechuic acid (**90**) were reported from the species *M. latifolia* for the first time. The chloroform extract from *M. glabra* leaves showed the highest inhibition activities with the IC_{50} values of 169.40 ± 9.30 and 303.64 ± 10.10 µg/mL against dipeptidyl peptidase-4 (DPP-4) and α-amylase, respectively. Among the compounds, the highest DPP-4 inhibition was presented by scopoletin (**64**) followed by pachypodol (**68**) with respective IC_{50} values of 36.34 ± 2.80 and 66.34 ± 2.30 µM. Meanwhile, halfordin (**88**) from *M. latifolia* was the most potent α-amylase inhibitor with an IC_{50} value of 195.27 ± 4.41 µM followed by stigmasterol (**56**) which exhibited an IC_{50} value of 304.02 ± 16.20 µM. This was supported by *in silico* docking analysis which revealed that scopoletin (**64**) exhibited the strongest binding (binding affinity of -7.3 kcal/mol) and showed the highest number of interactions with the amino acids that were critical for DPP-4 inhibition such as Ser630, Arg125, Tyr662, Tyr666, and Glu205 while halfordin (**88**) presented the highest number of interactions with critical amino acids of α-amylase such as His305, Thr163, Asp300, Trp59, Tyr62, and Trp58 with the binding affinity of -6.6 kcal/mol. Meanwhile, the strongest binding towards α-amylase was showed by stigmasterol (**56**) (binding affinity of -10.2 kcal/mol) which mainly formed hydrophobic interactions with the amino acids at the binding site. The *in silico* findings

in combination with *in vitro* activities suggested scopoletin (**64**), pachypodol (**68**), halfordin (**88**), and stigmasterol (**56**) as potential antidiabetic agents. The *in vivo* antidiabetic investigation of *M. glabra* chloroform leaves extract revealed that the dose of 200 mg/kg showed a more pronounced antidiabetic effect as compared to the lower doses of 50 and 100 mg/kg by lowering the blood glucose level in diabetic rats by 25.63%. The increment in glucagon-like peptide-1 (GLP-1) and insulin levels observed in the treated diabetic rats could be attributed to the DPP-4 inhibition property of the *M. glabra* extract as shown in the *in vitro* analysis. In conclusion, this study exhibited the potential of *M. glabra* and *M. latifolia* as the sources of antidiabetic alternatives or as natural therapies for the management of Type 2 diabetes mellitus.

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

KARAKTERISASI PERENCAT DPP-4 DAN α-AMILASE DARI *Melicope glabra* (Blume) T.G.Hartley DAN *Melicope latifolia* (DC.) T.G.Hartley (RUTACEAE) UNTUK TERAPI DIABETIK JENIS 2

Oleh

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Melicope glabra dan *Melicope latifolia* adalah tumbuhan dari keluarga Rutaceae yang boleh ditemui secara tempatan di Malaysia. Sehingga kini, laporan saintifik mengenai fitokimia dan bioaktiviti kedua-dua spesies masih terhad, terutamanya mengenai aktiviti antidiabetik. Dalam penyelidikan ini, potensi sifat antidiabetik dan komponen bioaktif *M. glabra* dan *M. latifolia* telah disiasat. Pengasingan fitokonstituen berpandukan ujian pada *M. glabra* memberikan lima sebatian iaitu *p*-geranyl asid kumarin (**49**), stigmasterol (**56**), scopoletin (**64**), evolitrine (**12**), dan pachypodol (**68**). Terutama, *p*-geranyl asid kumarin (**49**) dan evolitrine (**12**) telah diasingkan buat kali pertama daripada spesies *M. glabra.* Manakala empat sebatian telah diasingkan daripada *M. latifolia* iaitu β-sitosterol (**55**), halfordin (**88**), metil *p*-kumarat (**89**), dan asid protocatechuic (**90**). Halfordin (**88**), metil *p*-kumarat (**89**), dan asid protocatechuic (**90**) dilaporkan daripada spesies *M. latifolia* buat kali pertama. Ekstrak kloroform daripada daun *M. glabra* menunjukkan aktiviti perencatan tertinggi dengan nilai IC_{50} masing-masing 169.40 ± 9.30 dan 303.64 ± 10.10 μg/mL terhadap *dipeptidyl peptidase-4* (DPP-4) dan α-amilase. Di antara sebatian tersebut, perencatan DPP-4 tertinggi ditunjukkan oleh scopoletin (**64**) diikuti oleh pachypodol (**68**) dengan nilai IC_{50} masing-masing 36.34 ± 2.80 dan 66.34 ± 2.30 μM. Sementara itu, halfordin (**88**) daripada *M. latifolia* merupakan perencat α-amilase yang paling mujarab dengan nilai IC_{50} 195.27 ± 4.41 μM diikuti stigmasterol (**56**) yang menunjukkan nilai IC_{50} sebanyak 304.02 ± 16.20 μM. Ini disokong oleh analisis dok siliko yang mendedahkan bahawa scopoletin (**64**) mempamerkan pengikatan paling kuat (afiniti mengikat -7.3 kcal/mol) dan menunjukkan bilangan interaksi tertinggi dengan asid amino yang kritikal untuk perencatan DPP-4 seperti Ser630, Arg125, Tyr662, Tyr666, dan Glu205 manakala halfordin (**88**) mempersembahkan bilangan interaksi tertinggi dengan asid amino kritikal α-amilase seperti His305, Thr163, Asp300, Trp59, Tyr62, dan Trp58 dengan afiniti pengikat -6.6. kcal/mol. Sementara itu, ikatan paling kuat terhadap α-amilase ditunjukkan oleh stigmasterol (**56**) (afiniti mengikat -10.2 kcal/mol) yang terutamanya membentuk interaksi hidrofobik dengan asid amino di tapak

pengikatan. Penemuan in siliko dalam kombinasi dengan aktiviti in vitro mencadangkan scopoletin (**64**), pachypodol (**68**), halfordin (**88**), dan stigmasterol (**56**) sebagai agen antidiabetik yang berpotensi. Penyiasatan antidiabetik in vivo terhadap ekstrak daun *M. glabra* kloroform mendedahkan bahawa dos 200 mg/kg menunjukkan kesan antidiabetik yang lebih ketara berbanding dengan dos yang lebih rendah iaitu 50 dan 100 mg/kg dengan menurunkan paras glukosa darah dalam tikus diabetes dengan 25.63%. Peningkatan tahap *glucagon-like peptide-1* (GLP-1) dan insulin yang diperhatikan dalam tikus diabetes yang dirawat boleh dikaitkan dengan sifat perencatan DPP-4 ekstrak *M. glabra* seperti yang ditunjukkan dalam analisis in vitro. Kesimpulannya, kajian ini mempamerkan potensi *M. glabra* dan *M. latifolia* sebagai sumber alternatif antidiabetik atau sebagai terapi semula jadi untuk pengurusan diabetes mellitus Jenis 2.

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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 Doctor of Philosophy. The members of the Supervisory Committee were as follows:

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LIST OF ABBREVIATIONS

NHMS	National Health Morbidity Survey
T2DM	Type 2 Diabetes Mellitus
DPP-4	Dipeptidyl peptidase-4
IC_{50}	Half Maximal Inhibitory Concentration
FRAP	Ferric Reducing Antioxidant Power
TPC	Total Phenolic Content
TFC	Total Flavonoid Content
GAE	Gallic Acid Equivalent
RE	Rutin Equivalent
DPPH	1,1-Diphenyl-2-Picrylhydrazyl
CD	Concentration Dependent Cell Death
DM	Diabetes Mellitus
ROS	Reactive Oxygen Species
PPG	Post-prandial Hyperglycemia
GLP-1	Glucagon-like Peptide-1
GIP	Glucose-dependent Insulinotropic Polypeptide
mg	Milligram
kg	Kilogram
µg	Microgram
mL	Millilitre
dL	Decilitre
STZ	Streptozotocin
ALX	Alloxan
DNA	Deoxyribonucleic Acid
PDB	Protein Data Bank
NMR	Nuclear Magnetic Resonance
EI-MS	Electron Impact-Mass Spectra

FTIR	Fourier-transform Infrared
UATR	Universal Attenuated Total Reflection
1D	One-dimensional
2D	Two-dimensional
3D	Three-dimensional
^{1}H	Proton-1
^{13}C	Carbon-13
DEPT	Distortionless Enhancement by Polarization Transfer
COSY	Correlated Spectroscopy
HMQC	Heteronuclear Multiple Quantum Correlation
HMBC	Heteronuclear Multiple Bond Correlation
MHz	Megahertz
Hz	Hertz
δ	Chemical Shift
ppm	Parts Per Million
CC	Column Chromatography
$CHCl_3$	Chloroform
EtOAc	Ethyl Acetate
Methanol	MeOH
TLC	Thin Layer Chromatography
UV	Ultraviolet
nm	Nanometre
ASTM	American Society for Testing and Materials
M^+	Molecular Ion
m/z	Mass over Charge Ratio
%	Percent
H	Proton
C	Carbon
d	Doublet

J	Coupling Constant
t	Triplet
m	Multiplet
s	Singlet
dd	Doublet of Doublet
$CDCl_3$	Deuterated Chloroform
cm^{-1}	Wavenumber
λ	Wavelength
EtOH	Ethanol
m.p.	Melting Point
L	Litre
˚C	Degree Celcius
Acetone-d6	Deuterated Acetone
AMC	Gly-Pro-Aminomethylcoumarin
DMSO	Dimethyl Sulfoxide
µL	Microlitre
M	Molar
U	Unit
ID	Identity
ADT	Autodock Tools
Å	Angstrom
g	Gram
IACUC	Institutional Animal Care and Use Committee
CMC	Carboxymethylcellulose
HFD	High-fat Diet
mmol	Millimole
FBG	Fasting Blood Glucose
rpm	Revolutions Per Minute
OGTT	Oral Glucose Tolerance Test

AUC	Area Under the Curve
ELISA	Enzyme-linked Immunosorbent Assay
HRP	Avidin-Horseradish Peroxidase
ALT	Alanine Aminotransferase
APT	Aspartate Aminotransferase
ALP	Alkaline Phosphatase
TC	Total Cholesterol
TG	Triglycerides
LDL	Low-density Lipoprotein
HDL	High-density Lipoprotein
ANOVA	Analysis of Variance
^{3}J	Vicinal Coupling Constant
^{2}J	Germinal Coupling Constant
^{5}J	Long-range Coupling Constant
μM	Micromolar
RMSD	Root-Mean-Square Deviation
kcal	Kilocalorie
mol	Mole
Asp	Aspartic Acid
Glu	Glutamic Acid
Tyr	Tyrosine
Ile	Isoleucine
Val	Valine
Trp	Tryptophan
Leu	Leucine
His	Histidine
Thr	Threonine
Ala	Alanine
Ser	Serine

Arg	Arginine
Phe	Phenylalanine
OECD	Organization for Economic Co-operation and Development
CACC	Canadian Council on Animal Care

CHAPTER 1

INTRODUCTION

1.1 Research Background

Natural products have played a considerable role in the prevention and treatment of various ailments. The use of medicinal plants as an alternative treatment against diabetes has been described due to the presence of their bioactive components, such as coumarins, flavonoids, alkaloids, terpenoids, and phenolics (Tran et al., 2020). Rutaceae species including *Melicope lunu-ankenda*, *Murraya koenigii*, *Aegle marmelos*, and *Zanthoxylum armatum* were among the plants that were scientifically reported to exhibit antidiabetic properties (AL-Zuaidy et al., 2017; Mudi et al., 2017; Nurdiana et al., 2015; Rynjah et al., 2018).

Melicope glabra (Blume) T. G. Hartley and *Melicope latifolia* (DC.) T. G. Hartley are plants of Rutaceae family. *M. glabra* is an evergreen shrub or tree with the ability to grow up to 40 meters tall (Soepadmo, 1995). The plant can be found in Malaysia, Sumatra, Singapore, and Indonesia. In Malaysia, the plant is called by its local name "pepauh daun besar" or "tenggek burung". The aqueous decoction of its leaves is traditionally used for treatment of infections, fever, and cough by the Indonesian. Scientifically, *M. glabra* was reported to contain high phenolic contents and exhibited antioxidant activities (Kassim et al., 2013).

M. latifolia is a wild evergreen shrub that can be found in the primary and secondary forest of Sabah, Malaysia. The plant is also distributed in the Philippines, Indonesia, and Papua New Guinea. The common name of the plant is "kisampang" or "pepau", and the folklores in Indonesia used the plant for the relief of cramps and fever. A scientific study on *M. latifolia* reported that the plant has antiviral properties against hepatitis C virus (Wahyuni et al., 2013). Previous isolation studies of *M. glabra* and *M. latifolia* afforded various secondary metabolites, including flavonoids, coumarins, lignans, acetophenones, and alkaloids (Goh et al., 1990; Kassim et al., 2013; P. C. Lim et al., 2021; Saputri et al., 2018; Widyawaruyanti et al., 2021).

Currently, diabetes mellitus has emerged as a concerning metabolic disease. The number of people affected by diabetes mellitus were 463 million in 2019 and the number is expected to increase to 700 million in 2045 (Saeedi et al., 2019). According to National Health Morbidity Survey (NHMS) 2019, the diabetes prevalence in Malaysia has increased from 13.4% in 2015 to 18.3% in 2019. An approximated 3.9 million Malaysian adults aged 18 and above were diagnosed with diabetes, higher than 3.5 million in 2015 (Institute for Public Health 2020, 2019). The prevalence of Type 2 diabetes mellitus (T2DM) in Malaysia was reported to be the highest in Southeast Asia (Lasano et al., 2019).

Plant-based diabetic remedies have been the preferred choice of treatment in many developing countries due to their ease of availability, cost-effective, lesser side effects, and relative cultural familiarity and acceptance compared to the chemically synthesized drugs (Alqathama et al., 2020; Salehi et al., 2019; Tran et al., 2020). Medicinal plants with antioxidant activities are generally considered for the prevention of diabetes mellitus since oxidative stress is closely associated with the pathogenesis of T2DM. Phytochemicals such as coumarins, flavonoids, lignans, and phenolics have been reported as natural DPP-4 and α-amylase inhibitors.

1.2 Problem Statement

Post-prandial hyperglycemia (PPG) is one of the earliest abnormalities of T2DM and has garner attention for the treatment of T2DM due to its rate-limiting effect for attaining optimal glycemic control in patients of T2DM (Maffettone et al., 2018). Dipeptidyl peptidase-4 (DPP-4) and α-amylase inhibitors are the two different drugs that primarily target the minimization of PPG. However, diabetic patients have shown poor medication adherence to the currently available drugs mainly due to their side effects and cost. This issue has been one of the major contributing factors for poor glycemic control of diabetic patients which leads to morbidity and mortality (Polonsky & Henry, 2016).

Despite the potential secondary metabolites of *M. glabra* and *M. latifolia*, very limited scientific studies were traced concerning the biological activity and bioactive compounds of both *M. glabra* and *M. latifolia*, especially antidiabetic. A hypothesis was made that *M. glabra* and *M. latifolia* could be the potential candidates for management of T2DM based on their previously reported antioxidant activities and phytoconstituents.

As an effort in investigating the antidiabetic potential of *M. glabra* and *M. latifolia*, the *in vitro* antidiabetic assays including DPP-4 and α-amylase inhibitory assays were performed on the crude extracts, fractions, and isolated compounds of the plants. Assay-guided isolation approach was adopted in this study to obtain the DPP-4 and α-amylase inhibitors. *In silico* molecular docking was used to support the findings of *in vitro* study by predicting the binding affinity and interaction patterns between the potential compounds and enzyme receptors. Meanwhile, supplementary *in vivo* studies were carried out to show the pharmacological effects of the active extract in a combination of high-fat diet and low-dose streptozotocin-induced diabetic rat model.

1.3 Objectives

1.3.1 General Objectives

The general objectives of this study were to investigate the antidiabetic potential of *M. glabra* and *M. latifolia* against T2DM through the inhibition of DPP-4 and α-amylase and to identify the bioactive compounds.

1.3.2 Specific Objectives

The specific objectives of this study were to:

i. isolate and characterize the active constituents from the leaves of *M. glabra* and bark of *M. latifolia*.
ii. evaluate the dipeptidyl peptidase-4 (DPP-4) and α-amylase enzymes inhibition activity of crudes, fractions, and isolated constituents from the leaves of *M. glabra* and bark of *M. latifolia.*
iii. investigate the binding interaction between isolated constituents with dipeptidyl peptidase-4 (DPP-4) and α-amylase receptors via *in silico* study.
iv. investigate the *in vivo* antidiabetic activity of the most active crude in high-fat diet and streptozotocin-induced diabetic rat model.

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