UNIVERSITI PUTRA MALAYSIA

PHYTOCHEMICAL STUDIES AND IN VITRO, IN VIVO AND IN SILICO ANTIDIABETIC ACTIVITIES OF Paederia foetida L. EXTRACT

TAN DAI CHUAN

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By

TAN DAI CHUAN

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

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Chairman : Nur Kartinee Binti Kassim, PhD
Faculty : Science

Paederia foetida L. (Rubiaceae) is an edible plant distributed in Asian countries including Malaysia. Fresh leaves have been traditionally used to treat various diseases, including diabetes and as a remedy for indigestion and diarrhea. The plant has reported as antioxidant and antidiabetic properties. The plant is known as rich source of alkaloids, flavonoids, phenols, terpenoids etc. However, the bioactive compounds and the mechanisms of their beneficial effects have remained largely unknown particularly on the twig part of the plant. Therefore, the study covered the investigation of the enzyme inhibition (α-amylase, α-glucosidase, and dipeptidyl peptidase-4) of *Paederia foetida* twig extracts by *in vitro* assays, the identification of the phytoconstituents of *Paederia foetida* twigs, evaluation of the antidiabetic activity of *Paederia foetida* using high fat diet-low dose streptozotocin-induced Sprague Dawley rats model, and performance of *in silico* molecular docking of identified bioactive compounds. The chloroform extract showed the lowest *in vitro* α-amylase (9.60 µg/mL), α-glucosidase (245.6 µg/mL), and dipeptidyl peptidase-4 (DPP-4) (67.40%) inhibition activities compared to other extracts. The α-amylase and α-glucosidase inhibitory activity of the isolated compound, scopoletin had IC_{50} values of 0.052 and 0.057 mM, respectively. The chloroform extract also showed the highest total phenolic content among all the extracts. For the identification of antidiabetic compounds or enzyme inhibitors, assay guided isolation and metabolomics techniques were applied. Assay guided isolation technique revealed the chloroform extract as the most active extract and further purification afforded scopoletin as a bioactive antidiabetic compound. Meanwhile loading column scatter plot of orthogonal partial least square (OPLS) model in Gas Chromatography-Mass Spectrometry (GC-MS) metabolomics revealed the presence of 12 antidiabetic compounds, namely, dl-α-tocopherol, n-hexadecanoic acid, 2-hexyl-1-decanol, stigmastanol, 2-nonadecanone, cholest-8(14)-en-3-ol,4,4-dimethyl-,(3β,5α)-, stigmast-4-en-3-one, stigmasterol, 1-ethyl-1-tetradecyloxy-1-silacyclohexane, ɣ-sitosterol, stigmast-7-en-3-ol, (3β,5α,24S)-, and α-monostearin. For proton Nuclear Magnetic Resonance (^{1}H-NMR) metabolomics, the chloroform extract showed the presence of 13 antidiabetic compounds, campesterol, stigmasterol, β-sitosterol, ursolic acid, α-terpineol, lupeol, epifriedelinol, embelin, scopoletin, rutin, apigenin, geniposide, and linarin. The

standardization of the chloroform extract was carried out to identify the exact amount of the biomarker derived from the plant. The qNMR is a powerful analytical tool for the rapid and accurate determination of bioactive ingredients in herbal preparation. The validated qNMR method showed a good linearity ($r^2 = 0.9999$), limit of detection (0.009 mg/mL), and quantification (0.029 mg/mL), together with high stability (relative standard deviation = 0.022%), high precision (RSD < 1%), and good recovery (94.08%-108.45%). The *P. foetida* chloroform extract showed 7.34% scopoletin content, while the other extracts did not show any scopoletin content. The standardized extract was further evaluated for *in vivo* antidiabetic study at doses of 50 (Group 4) and 100 (Group 5) mg/kg and compared with 300 mg/kg metformin (Group 6). The *in vivo* results indicated that *P. foetida* extract of 50 mg/kg displayed the management of metabolic disorders of diabetic rats toward the normal state. The normal and obese rats displayed normal range of blood glucose levels while higher levels in diabetic rats. Groups 4, 5, and 6 showed significant decrement of blood glucose levels compared to diabetic rats (Group 3). There was 27.19% reduction of blood glucose level in Group 4 followed by 23.14% in Group 6 and then 16.79% in Group 5. Group 4 improved lipid profile, renal, and liver function as compared to Group 5 and 6. Group 4 showed reduction in the serum total cholesterol, triglycerides, low-density lipoproteins, uric acid, AST, and ALP and increase in high-density lipoprotein and total protein. Besides that, Group 4 exhibited good antioxidant activities in catalase (25.96 U/mg protein) and glutathione peroxidase (17.62 nmol/mg protein) analysis in the liver tissues, respectively. Group 4 also able to reduce the oxidative stress in protein carbonyl content and receptor for advanced glycation end-product markers. Molecular docking study was attempted to elucidate the mechanisms by which the active compounds could induce antidiabetic activities in α-amylase, α-glucosidase, and DPP-4. *In silico* calculations gave binding energy between scopoletin and α-amylase, α-glucosidase, and DPP-4 of -6.03, -2.92, and -6.1 kcal/mol, respectively. A total of two hydrogen bonds (Glu171 and Gly139) were observed in scopoletin-α-amylase complex along with one hydrophobic interaction (Ala169). The scopoletin-α-glucosidase complex showed two hydrogen bonding (Arg450 and Gln439) and one hydrophobic interaction (Tyr41). Besides that, one hydrogen atom in scopoletin showed a carbon-hydrogen bond to Ser360 in the DPP-4 enzyme. In conclusion, *P. foetida* exhibited enzyme inhibition *in vitro* and improved glucose and biochemical parameters in diabetic rats. This study suggested the potential of *P. foetida* as health promoting agent for Type 2 Diabetes Mellitus.

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

KAJIAN FITOKIMIA DAN AKTIVITI ANTIDIABETIK DALAM *IN VITRO*, *IN VIVO* DAN *IN SILICO* DARIPADA EKSTRAK *Paederia foetida* L.

Oleh

TAN DAI CHUAN

Mac 2021

Pengerusi : Nur Kartinee Binti Kassim, PhD
Fakulti : Sains

Paederia foetida L. (Rubiaceae) adalah tumbuhan yang boleh dimakan dan terdapat di negara-negara Asia termasuk Malaysia. Daun segar telah digunakan secara tradisional untuk merawat pelbagai penyakit termasuk diabetes dan sebagai ubat untuk senak dan cirit-birit. Tumbuhan ini telah dilaporkan sebagai sifat antioksidan dan antidiabetik. Tumhuhan ini dikenali terdapat sumber yang kaya, iaitu alkaloid, flavonoid, fenol, terpenoid, dan lain-lain. Walaubagaimanapun, sebatian bioaktif dan mekanisme kesan masih belum diketahui terutamanya di bahagian ranting tanaman. Oleh itu, kajian ini merangkumi penyiasatan dalam penghambatan enzim (α-amilase, α-glukosidase, dan dipeptidil peptidase-4) ekstrak ranting *Paederia foetida* dengan pengujian *in vitro*, pengenalpastian fitokonstituen ranting *Paederia foetida*, penilaian aktiviti antidiabetik *Paederia foetida* terhadap tikus berjenis Sprague Dawley yang diaruh diabetis mellitus melalui diet yang diet tinggi lemak, dan prestasi penyambungan molekul *in silico* sebatian bioaktif yang dikenal pasti. Ekstrak kloroform menunjukkan aktiviti perencatan *in vitro* yang terendah α-amilase (9.60 µg/mL), α-glukosidase (245.6 µg/mL), dan dipeptidil peptidase-4 (DPP-4) (67.40%) berbanding dengan ekstrak lain. Aktiviti penghambatan α-amilase dan α-glukosidase dari sebatian yang diasingkan, scopoletin mempunyai nilai IC50 masing-masing 0.052 dan 0.057 mM. Ekstrak kloroform juga menunjukkan jumlah kandungan fenolik yang tertinggi di antara semua ekstrak. Untuk mengenal pasti sebatian antidiabetik atau perencat enzim, teknik pengasingan berpandukan kajian bioaktiviti dan metabolomik telah digunakan. Teknik pengasingan berpandukan kajian bioaktiviti menunjukkan ekstrak kloroform sebagai ekstrak paling aktif dan pemurnian selanjutnya memberikan scopoletin sebagai sebatian antidiabetik aktif. Manakala hasil yang diperoleh daripada OPLS (*orthogonal partial least square*) dalam Kromatografi Gas-Spektrometri Jisim (GC-MS) menunjukkan 12 sebatian antidiabetik telah dikenalpasti, iaitu, dl-α-tocopherol, n-hexadecanoic acid, 2-hexyl-1-decanol, stigmastanol, 2-nonadecanone, cholest-8(14)-en-3-ol,4,4-dimethyl-,(3β,5α)-, stigmast-4-en-3-one, stigmasterol, 1-ethyl-1-tetradecyloxy-1-silacyclohexane, ɣ-sitosterol, stigmast-7-en-3-ol, (3β,5α,24S)-, dan α-monostearin. Dalam metabolomik proton Nuclear Magnetic Resonance (^{1}H-NMR), ekstrak kloroform menghasilkan 13 sebatian antidiabetik, campesterol, stigmasterol, β-sitosterol, ursolic acid, α-terpineol,

lupeol, epifriedelinol, embelin, scopoletin, rutin, apigenin, geniposide, dan linarin. Penyeragaman ekstrak kloroform dilakukan untuk mengenal pasti jumlah tepat biomarker yang berasal dari tumbuhan. qNMR adalah alat analisis yang kuat untuk penentuan bahan bioaktif dengan cepat dan tepat dalam penyediaan herba. Kaedah qNMR yang disahkan menunjukkan linearitas yang baik (r^2 = 0.9999), had pengesanan (0.009 mg/mL), dan kuantifikasi (0.029 mg/mL), bersama dengan kestabilan tinggi (sisihan piawai relatif = 0.022%), ketepatan tinggi (RSD <1%), dan pemulihan yang baik (94.08%-108.45%). Ekstrak kloroform *P. foetida* menunjukkan kandungan scopoletin sebanyak 7.34%, manakala ekstrak lain tidak menunjukkan kandungan scopoletin. Ekstrak standard dinilai dalam kajian antidiabetik *in vivo* dengan 50 (Kumpulan 4) dan 100 (Kumpulan 5) mg/kg dan dibandingkan dengan 300 mg/kg metformin (Kumpulan 6). Hasil *in vivo* menunjukkan bahawa 50 mg/kg ekstrak *P. foetida* dapat menguruskan gangguan metabolik tikus diabetik ke keadaan normal. Tikus normal dan gemuk menunjukkan tahap glukosa darah yang normal sementara tahap yang lebih tinggi pada tikus diabetik. Kumpulan 4, 5, dan 6 menunjukkan penurunan kadar glukosa darah yang ketara berbanding dengan tikus diabeti. Sebanyak 27.19% kadar glukosa darah dapat diturunkan dalam Kumpulan 4 diikuti oleh 23.14% pada Kumpulan 6 dan kemudian 16.79% pada Kumpulan 5. Kumpulan 4 meningkatkan profil lipid, fungsi ginjal, dan hati berbanding dengan Kumpulan 5 dan 6. Kumpulan 4 menunjukkan penurunan dalam jumlah kolesterol serum, trigliserida, lipoprotein berketumpatan rendah, asid urik, AST, dan ALP dan peningkatan lipoprotein berketumpatan tinggi dan protein total. Selain itu, Kumpulan 4 menunjukkan aktiviti antioksidan yang baik dalam katalase (25.96 U/mg protein) dan analisis glutathione peroxidase (17.62 nmol/mg protein) dalam tisu hati. Kumpulan 4 juga dapat mengurangkan tekanan oksidatif dalam kandungan karbonil protein dan reseptor untuk penanda akhir produk glikasi. Kajian terhadap melekular docking telah dijalankan untuk menjelaskan mekanisme antidiabetik yang mendorong sebatian tulen keatas aktiviti perencatan bagi α-amilase, α-glukosidase, dan DPP-4. Dalam pengiraan *in silico* memberikan tenaga pengikat antara scopoletin dan α-amilase, α-glukosidase, dan DPP-4 masing-masing -6.03, -2.92, dan -6.1 kcal/mol. Sebanyak dua ikatan hidrogen (Glu171 dan Gly139) diperhatikan dalam kompleks scopoletin-α-amilase bersama dengan satu interaksi hidrofobik (Ala169). Kompleks scopoletin-α-glukosidase menunjukkan dua ikatan hidrogen (Arg450 dan Gln439) dan satu interaksi hidrofobik (Tyr41). Selain itu, hanaya satu atom hidrogen dalam scopoletin menunjukkan ikatan karbon-hidrogen ke Ser360 dalam enzim DPP-4. Kesimpulannya, *P. foetida* menunjukkan penghambatan enzim *in vitro* dan peningkatan parameter glukosa dan bioakimia pada tikus diabetik. Kajian ini mencadangkan potensi *P. foetida* sebagai agen pemacu kesihatan untuk Diabetis 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:

Nur Kartinee binti Kassim, PhD
Senior Lecturer
Faculty of Science
Universiti Putra Malaysia
(Chairman)

Intan Safinar Ismail, PhD
Associate Professor
Faculty of Science
Universiti Putra Malaysia
(Member)

Muhajir Hamid, PhD
Associate Professor
Faculty of Biotechnology and Biomolecular Sciences
Universiti Putra Malaysia
(Member)

Norsuhana Omar, PhD
Medical Lecturer
School of Medical Sciences
Universiti Sains Malaysia, Health Campus
(Member)

ZALILAH MOHD SHARIFF, PhD
Professor and Dean
School of Graduate Studies
Universiti Putra Malaysia

Date: 10 June 2021

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DPPH	1,1-Diphenyl-2-picryl-hydrazyl
ABTS	2,2'-Azino-bis(3-ethylbenzothiazoline-6-sulfonic Acid)
DPPH	2,2-Diphenyl-1-picrylhydrazyl
TSP-d_4	3-(Trimethylsilyl)propionic-2,2,3,3-d_4 Acid Sodium Salt
DNS	3,5-Di-nitro Salicylic Acid
ALT	Alanin aminotransferase
Ala	Alanine
ALP	Alkaline Phosphatase
α	Alpha
Å	Angstrom
Arg	Arginine
Asn	Asparagine
AST	Aspartate aminotransferase
Asp	Aspartic Acid
AOAC	Association of Official Analytical Chemist
B	Beta
BMRB	Biological Magnetic Resonance Data Bank
BML	Birmingham Metabolite Library
BHA	Butylated Hydroxyanisole
BHT	Butylated Hydroxytoluene
CE-MS	Capillary Electrophoresis-Mass Spectrometry
C	Carbon
CMC	Carboxymethylcellulose
CAT	Catalase

ASP32	Catalytic Aspartic Residue
δ	Chemical Shift
.cdf	Computable Document Format
COSY	Correlated Spectroscopy
°C	Degree Celsius
$CDCl_3$	Deuterated Chloroform
DMSO	Dimethyl Sulfoxide
DMSO-d_6	Dimethyl Sulfoxide-d_6
ELISA	Enzyme-linked Immunosorbent Assay
FRAP	Ferric Reducing Antioxidant Power
FT-IR	Fourier Transformed Infrared Spectroscopy
γ	Gamma
GC-MS	Gas Chromatography-Mass Spectrometry
GA	Genetic Algorithm
GDM	Gestational Diabetes
GLDH	Glutamate Dehydrogenase
Glu	Glutamic Acid
Gln	Glutamine
GSH	Glutathione
GSSG	Glutathione Disulphide
GPx	Glutathione Peroxidase
Gly	Glycine
g	Gram
IC_{50}	Half Maximal Inhibitory Concentration
HMBC	Heteronuclear Multiple Bond Correlation
HMQC	Heteronuclear Multiple Quantum Correlation

HFD	High-Fat Diet
HDL	High-Density Lipoprotein
HPLC	High-Performance Liquid Chromatography
His	Histidine
HMDB	Human Metabolome Database
H	Hydrogen
IGT	Impaired Glucose Tolerance
ID	Inner Diameter
IS	Internal Standard
ICH	International Conference on Harmonization
IFCC	International Federation of Clinical Chemistry and Laboratory Medicine
ISE	Ion-Selective Electrode
kcal	Kilocalorie
LC_{50}	Lethal Concentration
Leu	Leucine
LOD	Limit of Detection
LOQ	Limit of Quantification
LC-MS	Liquid Chromatography-Mass Spectrometry
LDL	Low-Density Lipoprotein
RMSD	Lower Root-Mean-Square Deviation
Lys	Lysine
MQMCD	Madison-Quingdao Metabolomics Consortium Database
m/z	Mass over Charge Ratio
MS	Mass Spectrometry
λ_{max}	Maximum Wavelength

MHz	Mega Hertz
CD_3OD	Methanol-d_4
µg	Microgram
µL	Microlitre
µm	Micrometre
µM	Micromolar
mg	Milligram
mL	Millilitre
mm	Millimetre
mM	Millimolar
M	Molar Mass
mol	Mole
M^+	Molecular Ion
MUFAs	Monounsaturated Fatty Acids
MVDA	Multivariate Data Analysis
nm	Nanometre
NAFLD	Non-Alcoholic Fatty Liver Disease
NMR	Nuclear Magnetic Resonance
1D	One-Dimensional
OPLS	Orthogonal Partial Least Square
ppm	Part per Million
PLS	Partial Least Square
%	Percent
PPAR	Peroxisome Proliferator-Activated Receptor
Phe	Phenylalanine
π	Pi

PNPG	p-Nitrophenyl-α-d-glucopyranoside
PPHG	Post-Prandial Hyperglycaemia
pH	Potential of Hydrogen
PCA	Principal Component Analysis
Pro	Proline
PCO	Protein Carbonyl Content
PDB	Protein Data Bank
PKC	Protein Kinase C
Q	Quadrupole
qNMR	Quantitative Nuclear Magnetic Resonance
ROS	Reactive Oxygen Species
RAGE	Receptor of Advanced Glycation End-products
RBCs	Red Blood Cells
R_f	Refractive
RSD	Relative Standard Deviation
RT	Retention Time
Ser	Serine
SGPT	Serum Glutamic Pyruvic Transaminase
SGOT	Serum Glutamic-Oxaloacetic Transaminase
SD	Standard Deviation
SE	Standard Error
STZ	Streptozotocin
TLC	Thin Layer Chromatography
Thr	Threonine
TOF	Time-of-Flight
TC	Total Cholesterol

TIC	Total Ion Chromatogram
TG	Triglycerides
Trp	Tryptophan
2D	Two-Dimensional
Tyr	Tyrosine
UPLC-MS	Ultra-Performance Liquid Chromatography-Mass Spectrometry
UV-vis	Ultraviolet-visible
USDA	United States Department of Agriculture
USFDA	United States Food and Drug Administration
UATR	Universal Attenuated Total Reflection
Val	Valine
VIP	Variable Importance of Projection
VLDL	Very Low-Density Lipoprotein
WBC	White Blood Cells
WHO	World Health Organization
GIP	Glucose-dependent Insulinotropic Peptide
^{15}N	Nitrogen-15
^{13}C	Carbon-13
DPP-4	Dipeptidyl Peptidase-4
^{1}H	Hydrogen-1
GLP-1	Glucagon-Like Peptide-1
BPX5	5% Phenylmethylsilane
T1DM	Type 1 Diabetes Mellitus
BACE1	β-site Amyloid Precursor Protein Cleaving Enzyme 1
GLUT2	Glucose Transporter 2
T2DM	Type 2 Diabetes Mellitus

CHAPTER 1

INTRODUCTION

Natural products are chemical compounds produced by plants, animals, marine, and microorganism. Plant metabolites of the natural products consist of primary and secondary metabolites. During the growth process, primary metabolites are produced due to energy metabolism, such as carbohydrates, amino acids, ethanol, and lactic acid. Secondary metabolites are organic compounds which are not directly involved in the normal growth, development, or reproduction of an organism (R. Tiwari & Rana, 2015). The secondary metabolites are classified into five major classes, including phenolics, alkaloids, saponins, terpenes, and lipids.

Medicinal plants are natural antioxidants and effective herbal medicines. The use of the medicinal plants to treat diabetes has been reported since ancient time (D.-G. Han et al., 2019). A medicinal plant called *Paederia foetida*, locally known as "Pokok Seketunt", is a semi-woody climber belonged to Rubiaceae family, which can be found in India, Malaysia, China, Japan, Philippines, and other Asian countries. The leaves and twigs of the plant are reported to treat diabetes mellitus.

Diabetes mellitus is common non-communicable disease which is increasing all over the world (Ministry of Health Malaysia, 2015). The trend of diabetes is increasing gradually in Malaysia. Based on the National Health and Morbidity Survey 2019 by the Minister of Health, the prevalence of the diabetes in adult population in Malaysia has increased from 13.4% in 2015 to 18.3% in 2019, with blood sugar level of 7.0 mmol/L or above (Ministry of Health Malaysia, 2020). An estimated 3.9 million adults in Malaysia aged 18 and above had diabetes as of last year, higher than 3.5 million in 2015 (Ministry of Health Malaysia, 2020). There are two types of diabetes commonly exist, Type 1 and Type 2 diabetes mellitus.

The antidiabetic research using medicinal plant has been practiced by mankind for more than 10 years. The conventional drugs are thought to have more adverse effects in the recent time and hence the medicinal plant are more wanted by the public (Sandhaanam & Pandikumar, 2019; Shan et al., 2007). However, the recent limitations of the herbal medicine are the lack of standardization and no verification of biomarker in the medicinal plant. Due to the inherent variability of the constituents of herbal medicine, it is generally difficult to establish quality control parameter and maintain consistent batch-to-batch quality (Ghosh, 2018). Therefore, the standardization and identification of biomarker in the plant extract are very important to commercialize the herbal products. Standardization is the body of information and control necessary to product material of reasonable consistency. This achieved through the minization of the inherent variation of natural product composition by the quality assurance practices (Bijauliya et al., 2017).

According to the above-mentioned information, as part of the ongoing effort to discover potential bioactive compounds from the plant as an alternative treatment for diabetes, *Paederia foetida* was selected for the investigation based on their rich chemistry and history of providing bioactive compounds responsible to the ethno-medicinal uses. Thus, the plant was opted for this work as the literature study showed that they possess a great deal of potential phytochemical constituents that are worthwhile to be further studied.

Antidiabetic property of the plants were verified by *in vitro* testing of the plant extracts obtained from two different locations (Ledang, Johor and Termeloh, Pahang) against three assays, namely α-amylase, α-glucosidase, dipeptidyl peptidase-4 (DPP-4) inhibition. Secondly, the identification of phytochemical responsible for antidiabetic property of the plant using assay guided isolation and metabolomics approaches. Thirdly, standardization of the plant extracts by qNMR and UV-vis spectrophotometer. Lastly, the verification of antidiabetic property of the plant using an animal model. Sprague Dawley rats were used to mimic the Type 2 diabetes mellitus conditions and were treated with *Paederia foetida* standardized extract and compared with metformin as standard. To understand the mechanism of antidiabetic action, *in silico* molecular docking analysis was performed. The potential antidiabetic compounds were docked onto α-amylase, α-glucosidase, DPP-4 enzymes.

The objectives of the study were to:

i. investigate the enzyme inhibition (α-amylase, α-glucosidase, and dipeptidyl peptidase-4) activities of *Paederia foetida* twig extracts
ii. identify the phytoconstituents and biomarkers of *Paederia foetida* twigs
iii. standardize and quantify scopoletin in *Paederia foetida* active extract
iv. evaluate the *in vivo* antidiabetic activity of *Paederia foetida* on high fat diet-low dose streptozotocin induced Sprague Dawley rats
v. perform *in silico* molecular docking of selected bioactive compounds

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