UNIVERSITI PUTRA MALAYSIA

METABOLITE PROFILING AND CHARACTERIZATION OF Lupinus albus L. AND ITS CORRELATION WITH ANTIOXIDANT AND ALPHA-GLUCOSIDASE INHIBITORY ACTIVITIES

HELLAL KHAOULA

FSTM 2021 6

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By

HELLAL KHAOULA

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

January 2021

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بِسْمِ اللَّـهِ الرَّحْمَـٰنِ الرَّحِيمِ

(قُلْ إِنَّ صَلَاتِي وَنُسُكِي وَمَحْيَايَ وَمَمَاتِي لِلَّهِ رَبِّ الْعَالَمِينَ)

Say, “Indeed, my prayer, my rites of sacrifice, my living and my dying are for Allah, Lord of the worlds”.

Al An’am 162 (QS 6: 162)

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DEDICATION

This dissertation is lovingly dedicated to my angel mother “Hassina”. Whose love, devotion, dua’a, and scarification have been the strength of my striving. All that I am or ever hope to be, I owe it to her.

"إلى التي نجتني تمتماتها على سجادة الصلاة من أشياء لا يعلمها إلا الله، واستطاعت وحدها أن تكون الجميع.. إلى أمي"

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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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By

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January 2021

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Faculty : Food Science and Technology

Diabetes mellitus (DM) is the most widely recognized endocrine disorder in almost all countries. Due to the adverse effects of modern treatment such as hypoglycemic coma, renal complications, stomach upset, and weight gain, the use of medicinal plants as antidiabetic agents has been gaining increasing attention due to their effectiveness. The main objective of this study was to profile and characterize the metabolites presence in the Algerian medicinal food plants that are traditionally used for the treatment of hyperglycemia (*Peganum harmala*, *Zygophyllum album*, *Anacyclus valentinus*, *Ammodaucus leucotrichus*, *Lupinus albus*, and *Marrubium vulgare).* To achieve that aim, this study was carried out in several phases. In the first phase, we aimed to screen the DPPH free radical scavenging, α-glucosidase and nitric oxide inhibitory activities as well as total phenolic content (TPC) of the six Algerian medicinal food plants extracted using different percentage of ethanol (0, 50, 80, and 100%). The findings revealed that the highest TPC of 612.84 µg GAE/mg extract was observed in *M. vulgare* extracted with 80% ethanol. The 100% ethanol extract of *A. leucotrichus* exhibited the highest free radical scavenging activity with an IC_{50} value of 26.26 µg/mL. However, the 100% ethanol extract of *L. albus* seeds was found to be the most potent in inhibiting α-glucosidase activity with the lowest IC_{50} value of 6.45 µg/mL. Therefore, it was the best candidate for further investigation in the next phase where the metabolite profiling was conducted using proton nuclear magnetic resonance (^{1}H NMR) spectroscopy. A partial least square analysis (PLS) was used to assess the relationship between the α-glucosidase inhibitory activity of *L. albus* and the metabolites identified in the extract. Based on the PLS model, isoflavonoids, amino acids, and several fatty acids were identified as metabolites that contributed to the inhibition of α-glucosidase. The PLS model exhibited a perfect goodness of fit where (R^2Y (cum) > 0.9) and predictive quality (Q^2(cum) > 0.9). For further investigation, the metabolite profile was carried out by using ultra-high-performance liquid chromatography-electrospray ionization-tandem mass spectrometry (UHPLC-ESI-MS/MS) technique in both negative and positive ion mode. A total of 45 metabolites were tentatively identified by means of MS data, together with the

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interpretation of the observed MS/MS spectra in comparison with those found in the literature. Consequently, in the next part of the study, the 100% ethanolic extract of *L. albus* seeds was fractionated with different solvent polarity using solid phase extraction (SPE) and the DPPH free radical scavenging, and α-glucosidase inhibitory activities of the resulted fractions were evaluated. This phase provides useful information for the identification of compounds in *L. albus* seeds fractions by NMR based metabolomics. In total, 35 metabolites were identified from *L. albus* seeds fractions. Principal component analysis (PCA) is used as a multivariate projection method for visualizing the different composition of four different fractions. Among the fractions studied, the chloroform fraction (CF) exhibits a high free radical scavenging (DPPH) and α-glucosidase inhibitory activities with IC_{50} values of 24.08 and 20.08 µg/mL, respectively. A PLS model has been successfully performed to correlate the potential active metabolites with the corresponding biological activities. Metabolites such as proline, caprate, asparagine, lupinoisolone C, hydroxyiso-lupalbigenin and some unknown compounds showed high correlation with the bioactivities studied. Autofit of SIMCA treatment exhibited a perfect goodness of fit with R^2Y (cum) > 0.9 and a predictive quality of Q^2 (cum) > 0.9. Moreover, a total of 25 metabolites were tentatively identified from CF using UHPLC-ESI-MS/MS analysis by comparison with previously reported data. The last phase of this study has been undertaken with the aim to isolate and characterize active metabolites from CF through chromatography techniques. Five compounds including, triolein (**2**), lupeol (**3**), β-sitosterol (**4**), betulinic acid (**5**), and ursolic acid (**13**) were isolated from CF. All compounds found to have both α-glucosidase inhibitory and DPPH free radical scavenging activities. Triolein (**2**) was found to possess the highest α-glucosidase inhibition activity with IC_{50} value of 3.32 µg/mL, while ursolic acid (**13**) exhibited the strongest DPPH free radical scavenging inhibitor with IC_{50} value of 13.97 µg/mL. In summary, the findings of this research suggest that *L. albus* seeds extracts exert antidiabetic activity through their effects as antioxidant and α-glucosidase inhibitors. Triolein, lupeol, β-sitosterol, betulinic acid, and ursolic acid can be contributed to the antidiabetic activity exhibited by *L. albus* seeds extracts. The outcomes obtained endorse the claims that *L. albus* seeds extract can be beneficial in the prevention and treatment of diabetes and its associated disorders. To the best of our knowledge, this fingerprint profile is the first extensive study of metabolites from *L. albus* seeds extract fractions, which may explain the use of *L. albus* as antidiabetic agent in the Algerian folk medicine and its application in future phytomedicinal preparations for the treatment of diabetes.

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PROFIL DAN PENCIRIAN METABOLIT *Lupinus albus* L. DAN HUBUNGANNYA DENGAN AKTIVITI ANTIOKSIDAN DAN PERENCATAN α-GLUKOSIDASE

Oleh

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Diabetes mellitus (DM) merupakan penyakit endokrin yang paling dikenali hampir seluruh negara. Oleh kerana kesan buruk dari rawatan moden seperti koma hipoglikemik, komplikasi buah pinggang, sakit perut, dan kenaikan berat badan, penggunaan tanaman ubatan sebagai agen antidiabetes semakin mendapat perhatian kerana keberkesanannya. Objektif utama kajian ini adalah untuk memprofil dan mencirikan metabolit yang wujud dalam tumbuhan makanan ubatan Algeria yang digunakan secara tradisional untuk rawatan hiperglisemia (*Peganum harmala*, *Zygophyllum album*, *Anacyclus valentinus*, *Ammodaucus leucotrichus*, *Lupinus albus,* dan *Marrubium vulgare*). Untuk mencapai tujuan tersebut, kajian ini dilakukan dalam beberapa fasa. Pada fasa pertama, kami telah menyaring aktiviti pemerangkapan radikal bebas DPPH, perencatan α-glukosidase dan nitrik oksida serta jumlah kandungan fenol (TPC) terhadap enam tumbuhan makanan ubatan Algeria yang diekstrak dengan peratusan etanol yang berbeza (0, 50, 80 dan 100%). Hasil kajian menunjukkan bahawa TPC tertinggi iaitu 612.84 µg GAE / mg ekstrak diperhatikan pada *M. vulgare* yang diekstrak dengan etanol 80%. Ekstrak etanol 100% *A. leucotrichus* memperlihatkan aktiviti pemerangkapan radikal bebas tertinggi dengan nilai IC_{50} 26.26 µg / mL. Walau bagaimanapun, ekstrak etanol 100% biji *L. albus* telah didapati paling kuat dalam menghalang aktiviti α-glukosidase dengan nilai IC_{50} terendah 6.45 µg / mL. Oleh itu, ia adalah calon terbaik untuk penyelidikan lebih lanjut pada fasa seterusnya di mana profil metabolit dijalankan menggunakan spektroskopi resonans magnetik nuklear proton (1H NMR). Analisis kuasa dua terkecil separa (PLS) telah digunakan untuk menilai kolerasi antara aktiviti perencatan α-glukosidase dan metabolit yang dikenal pasti dari ekstrak *L. albus*. Berdasarkan model PLS, isoflavonoid, asid amino, dan beberapa asid lemak telah dikenal pasti sebagai metabolit yang menyumbang kepada perencatan aktiviti α-glukosidase. Model PLS memperlihatkan kebaikan yang sesuai di mana (R^2Y (cum)> 0.9) dan kualiti ramalan (Q^2 (cum)> 0.9). Untuk penyelidikan lebih lanjut, profil metabolit telah dilakukan dengan menggunakan teknik kromatografi cecair prestasi tinggi-pengionan secara semburan elektro-spektrometri jisim (UHPLC-ESI-MS/MS)

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dalam mod ion negatif dan positif. Sebanyak 45 metabolit telah dikenal pasti melalui data MS, bersama dengan tafsiran spektrum MS/MS yang telah dibandingkan dengan kajian terdahulu. Oleh itu, pada kajian seterusnya, pengekstrakan 100% etanol biji *L. albus* telah difraksionasi dengan polariti pelarut yang berbeza menggunakan pengekstrakan fasa pepejal (SPE) dan aktiviti pemerangkapan radikal bebas DPPH dan rencatan α-glukosidase dari fraksi yang dihasilkan telah dinilai. Fasa ini memberikan maklumat berguna untuk mengenal pasti sebatian dalam fraksi *L. albus* menggunakan kaedah metabolomik berasaskan NMR. Secara keseluruhan, 35 metabolit telah dikenal pasti dari fraksi biji *L. albus*. Analisis komponen utama (PCA) telah digunakan sebagai kaedah unjuran multivariat untuk menggambarkan komposisi empat fraksi yang berbeza. Di antara fraksi yang dikaji, fraksi kloroform (CF) menunjukkan aktiviti pemerangkapan radikal bebas (DPPH) dan rencatan α-glukosidase tertinggi dengan nilai IC_{50} masing-masing adalah 24.08 dan 20.08 µg/mL, masing-masing. Satu model PLS telah berjaya dilaksanakan untuk menghubungkan metabolit aktif yang berpotensi dengan tindak balas aktiviti biologi. Metabolit seperti prolin, kaprat, asparagina, lupinoisolone C, hydroxyiso-lupalbigenin dan beberapa sebatian yang tidak diketahui menunjukkan penyumbang yang tinggi terhadap bioaktiviti yang dikaji. Kaedah autofit SIMCA menunjukkan kebaikan sesuai dengan R^2Y (cum)> 0,9 dan kualiti ramalan Q^2 (cum)> 0,9. Tambah pula, sebanyak 25 metabolit telah dikenal pasti dari CF menggunakan analisis UHPLC-ESI-MS / MS dengan membandingkan laporan data terdahulu. Fasa terakhir kajian ini dilakukan dengan tujuan untuk memencilkan dan mencirikan metabolit aktif dari CF melalui teknik kromatografi. Lima sebatian termasuk, triolein (2), lupeol (3), β-sitosterol (4), asid betulinik (5), dan asid ursolik (13) telah dipencilkan dari CF. Semua sebatian didapati mempunyai aktiviti rencatan α-glukosidase dan pemerangkapan radikal bebas (DPPH) . Triolein (2) didapati mempunyai aktiviti perencatan α-glukosidase tertinggi dengan nilai IC_{50} 3.32 µg/mL dan asid ursolik (13) memiliki aktiviti pemerangkapan radikal bebas DPPH terkuat dengan nilai IC_{50} 13.97 µg/mL. Ringkasnya, hasil kajian ini menunjukkan bahawa ekstrak biji *L. albus* menunjukkan aktiviti antidiabetik melalui kesannya sebagai perencat antioksidan dan α-glukosidase. Triolein, lupeol, β-sitosterol, asid betulinic, dan asid ursolic boleh menjadi penyumbang kepada aktiviti antidiabetik yang ditunjukkan oleh ekstrak biji *L. albus*. Hasil yang diperoleh menyokong dakwaan bahawa ekstrak biji *L. albus* memberi manfaat dalam pencegahan dan rawatan diabetes dan penyakit yang berkaitan dengannya. Sepengetahuan kami, profil cap jari ini adalah kajian pertama mengenai metabolit dari fraksi ekstrak biji *L. albus*, yang mungkin dapat menerangkan kegunaan *L. albus* sebagai agen antidiabetik dalam perubatan rakyat Algeria dan aplikasinya dalam persediaan fitoubatan pada masa hadapan untuk rawatan diabetes.

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

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LIST OF ABBREVIATIONS

ANOVA	Analysis of variance
Br	Broad
CC	Column chromatography
CF	Chloroform fraction
$CHCl_3$	Chloroform
COSY	Correlation spectroscopy
d	Doublet
dd	Doublet of doublet
DM	Diabetes Mellitus
DMSO	Dimethyl sulfoxide
DMSO-d_6	Deuterated dimethyl sulfoxide
DPPH	2,2-diphenyl-1-picrylhydrazyl free radicals
DW	Dry weight
EtOAc	Ethyl acetate
EF	Ethyl acetate fraction
ESI	Electrospray ionization
GAE	Gallic acid equivalent
GC MS	Gas chromatography- mass spectrometry
HF	Hexene fraction
HMBC	Heteronuclear multiple-bond correlation
HSQC	Heteronuclear single-quantum correlation
Hz	Hertz
IC_{50}	Inhibition concentration at 50 percent
J	Coupling constant in Hz

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LC MS	Liquid chromatography–mass spectrometry
m	Multiple
m/z	Mass to charge ratio
MeOH	Methanol
MF	Methanol fraction
mHz	MegaHertz
mL	Milliliter
mm	Millimeter
MS	Mass spectrometry
MS/MS	Tandem mass spectrometry
MTT	3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl tetrazolium bromide
NMR	Nuclear magnetic resonance
PCA	Principal component analysis
PLS	Partial least squares
ppm	Part per million
PNPG	p-nitrophenyl-α-D-glucopyranose
Rt	Retention time
s	Singlet
SPE	Solide phase extraction
t	Triplet
TIC	Total ion chromatogram
TLC	Thin layer chromatography
TPC	Total phenolic contents
UHPLC-MS/MS	Ultra-high performance liquid chromatography tandem mass spectrometry analysis

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WHO	World health organization
δ	Chemical shift in ppm
1D	One-dimensional
^{1}H	Proton
2D	Two-dimensional
^{13}C	Carbon-13

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CHAPTER 1

INTRODUCTION

1.1 Background

Diabetes mellitus (DM) is the most worldwide common metabolic disorder with life threatening complications. According to the recent data from the World Health Organization (WHO) and International Diabetes Federation (IDF), the prevalence of diabetes has increased dramatically over recent years. Currently, around 463 million people in the world (1 in 11 of the world's adult population) are diabetics, and this number is anticipated to witness significant growth to hit 700 million by 2045 (IDF, 2019). Moreover, 46% of people with diabetes are undiagnosed. Commonly used drugs for the treatment of DM include chemically synthesized hypoglycemic agents such as biguanides, sulphonylurea, and α-glucosidase inhibitors show adverse effects such as hypoglycemic coma, renal complications, stomach upset, and weight gain (Kasturi et al., 2017). Therefore, due to other historical, cultural, and economic reasons, people are diverging toward herb-based drugs and natural sources to help in the treatment of several diseases including diabetes (Azwanida, 2015). The use of medicinal plants as antidiabetic agents has been gaining increasing attention due to their effectiveness. The latter is strongly supported by several empirical therapies and clinical experiences accumulated over hundreds of years (Alamgir, 2017).

According to United Nations Environment Program, a significant number of spontaneous species in North Africa within Algeria have potential value in terms of medicine. For instance, Algerian folk medicine has been practiced for centuries, and local populations still relay on traditional healers to treat several ailments. Being a land of edaphic potentials and diverse climatic that vary between the Mediterranean climate in the north, semi-arid climate in the high steppe plains, and arid across the Sahara, allow several of such indigenous, exotic, and essential plants to grow luxuriously in Algeria (Ouelbani et al., 2016). A large collection of natural resources with more than 3164 plant species can be distinguished in the Algerian flora (Rachid et al., 2012). However, only few systematic chemical and pharmacological studies have been performed on these species (Benarba, 2016). Although, folk medicine is based on traditional scriptures, pharmacopeias and clinical experience collected over hundreds of years, scientific investigations of the particular components having therapeutic effect is strongly needed, especially for the treatment of chronic diseases such as diabetes (Al-Aboudi and Afifi, 2011).

As per the ethnobotanical literature on traditional phytotherapy of Algerian medicinal plants, the species including *Peganum harmala*, *Zygophyllum album*, *Anacyclus valentinus*, *Ammodaucus leucotrichus*, *Lupinus albus*, and *Marrubium vulgare* are consistently used by the tribal communities for the treatment of diabetes. The premier steps before use the biologically active compound from the target plant resources is begin by extraction, pharmacological screening, isolation and characterization of bioactive

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compound, then clinical evaluation. In several cases, the use of the plants and their respective therapeutic prescription in popular medicine are not easy to understand and we can question if there is a relation between the therapeutic properties of these plants and their inhibitory effects. To answer this question, a series of bioassay guided were performed using the selected plants to screen their free radical scavenging (DPPH) and α-glucosidase and nitric oxide (NO) inhibitory activities, as well as the total phenolic content (TPC).

Metabolomics, the large-scale study of small metabolites in biological specimens, allows simultaneously qualitative and quantitative measurement in a single experiment and provides a wealth of biological information on complex system by relating biological endpoints to multiple altered metabolite concentrations (Liu & Locasale, 2017). Metabolomics is a powerful approach that has been applied in many fields including plant toxicology, plant science, nutrition and systems biology (Zhang et al., 2012). A range of analytical tools has been employed to analyze metabolites. Among those, nuclear magnetic resonance (NMR) and mass spectrometry (MS) coupled to different chromatographic separation techniques, such as liquid or gas chromatography are highly sophisticated and sensitive tools for the simultaneously analysis of a large number of metabolites (Emwas et al., 2019). One of the qualities of mass spectrometry is that little amounts of sample are needed, so it would be extremely effective to be able to obtain as much structural information from a single mass spectrum (Bouslimani et al., 2014). Modern mass spectrometry is continuing to be used excitingly, not only in early medicinal exploration or other biotechnological uses, yet additionally for the discovery of natural products. Coupled techniques such as LC NMR or LC MS unquestionably allowed online structure elucidation and provided impressive examples of metabolite recognition, however, the necessity to get the purified compounds in hand is still in need (Emwas et al., 2019).

1.2 Problem statements

Diabetes is a chronic devastating illness which, threats millions of persons worldwide. Even with the appropriate symptomatic and the curative advance, diabetes without a side effect still a big challenge for researchers. The presence of serious side effects of conventional antidiabetic medications such as hypoglycemic coma, renal complications, stomach upset, and weight gain rises the scientific interests to study plant bioactive compounds that focused upon disease treatment and strategies for prevention with less toxic effect. The selected plants *Peganum harmala*, *Zygophyllum album*, *Anacyclus valentinus*, *Ammodaucus leucotrichus*, *Lupinus albus*, and *Marrubium vulgare* from arid areas are a good source of medicinal plants that were widely used in the traditional medicine systems of many cutlers over hundreds of years. However, there is still a scarce of pharmaceutical screening reports that ties the bioactive constituents responsible of the antidiabetic abilities to efficacy. Furthermore, compound identification is a major bottleneck in the natural product studies. Thus, combining NMR- and MS-metabolomics approaches may expand the frontiers of chemical assessment of the metabolites correlated with the hypoglycemic properties of diverse medicinal species.

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1.3 Objectives

To address the aforementioned problems, the present study was designed and conducted, with the goal to seek for the bioactive compounds to be used for the management of diabetes and its complications. To achieve this goal, this study embarks to the four specific objectives:

1. To screen the effect of different ethanol ratios on DPPH free radical scavenging, α-glucosidase and nitric oxide inhibitory activities of six Algerian traditional medicinal plant extracts.
   (*From the screening activities in Objective 1, Lupinus albus was identified as having the highest activity, thus was selected for further study*)

2. To determine the bioactive compounds in *Lupinus albus* extract by using ^{1}H NMR-metabolomics approach and UHPLC-ESI-MS/MS.

3. To diffrentiate the metabolome of *L. albus* fractions and correlate their chemical profiles with biological activities by using ^{1}H NMR-metabolomics, as well as to profile the bioactive fraction using UHPLC-ESI-MS/MS.

4. To isolate and elucidate the bioactive compounds from *L. albus* fraction using bioassays guided isolation and to evaluate the biological activities of the isolated compounds.

1.4 Hypothesis

The current research was undertaken to create an inventory of the plants used in Algeria by traditional healers to cure diabetes. The selected Algerian endemic species may contain several bioactive compounds that contribute to their health benefits against diabetes mellitus. The values obtained could indicate that these plants can be investigated in pharmacotherapeutic for eventual treatment. The phenolic compounds presented in these plants after optimizing the processing methods may also serve as lead compounds for the synthesis of a series of inhibitors. Furthermore, it is expected that combination of the ^{1}H NMR spectroscopy and UHPLC-ESI-MS/MS could enhance the number of identified metabolites from the plant sample. On the other hand, fractionation using the solid-phase extraction (SPE) is a simple method that allowing the access to more selective and easy-to-use phases in order to reduce in one step the amount of sample to deal with and to simplify the analytical procedures. This research focused as well on the evaluation of the bioactivities of the isolated compounds from the active fractions which might pave the way for future studies on antidiabetic potency of the active plant.

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LIST OF PUBLICATIONS

Hellal, K., Maulidiani, M., Ismail, I. S., Tan, C. P., & Abas, F. (2020). Antioxidant, α-Glucosidase, and Nitric Oxide Inhibitory Activities of Six Algerian Traditional Medicinal Plant Extracts and ^{1}H-NMR-Based Metabolomics Study of the Active Extract. *Molecules*, 25(5), 1247.

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