UNIVERSITI PUTRA MALAYSIA

BIOLOGICAL ACTIVITIES, PHYTOCHEMICAL ANALYSIS AND ISOLATION OF BIOACTIVE COMPOUNDS OF Arbutus pavarii Pamp

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By

BUZGAIA NAWAL M BUBAKER

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

May 2020

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)

DEDICATION

This thesis is dedicated to my husband, parents, children and all my family.

Abstract of thesis presented to the Senate of Universiti Putra Malaysia, in Fulfilment of the requirement for the degree of Doctor of Philosophy

BIOLOGICAL ACTIVITIES, PHYTOCHEMICAL ANALYSIS AND ISOLATION OF BIOACTIVE COMPOUNDS OF *Arbutus pavarii* Pamp

By

BUZGAIA NAWAL M BUBAKER

May 2020

Chairman : Professor Khozirah binti Shaari, PhD
Institute : Bioscience

Natural products from plants have been used for centuries in folklore to treat and prevent various diseases and ailments. The development of drugs is mostly based on natural products and currently researchers focus on plants resources to find out more valuable pharmaceutical drugs. According to recent data from the world health organization (WHO), two thirds of modern drugs are originated from plants. The genus *Arbutus* (*Ericaceae*) has been used traditionally in folk medicine due to its phytomedicinal properties, especially *Arbutus pavarii*. However, this selected plant still not evaluated for its efficacy, quality and consistency to support its traditional uses specifically in treating diabetes. Despite the previous studies revealed the biological activities of *A. pavarii* as antibacterial, antioxidant and α-glucosidase inhibitor agent, but there is still a scarce of scientific reports about the bioactive compounds that contribute to its health benefits. The main aim of this study was the investigation of *A. pavarii* Pamp as a potent source of beneficial bioactive compounds. Therefore, this research focused on the profiling and identification of metabolites in methanol crude extracts and fractions of the leaf and stem bark to evaluate their capabilities for antimicrobial, antioxidant and α-glucosidase inhibitory activities. To achieve that, series of bioassay-guided extraction and isolation protocols were performed. The crude extracts and solvent fractions of the leaf and the stem bark were tested against Methicillin-resistant *Staphylococcus aureus* (MRSA). The extracts were fractionated using liquid-liquid partition (LLP) to obtain hexane, chloroform, ethyl acetate, and butanol fractions. The isolation procedures guided by the bioassay results thin layer chromatography-bioautographic (TLC-bioautographic) and disk diffusion were accomplished using advanced chromatography techniques in order to purify the bioactive chemical constituents. The methanol extracts and solvent fractions of the leaf and the stem bark were also evaluated for total phenolic contents (TPC), total flavonoid content (TFC), radical scavenging assay (DPPH) free radical scavenging, ferric reducing antioxidant power (FRAP) and α-glucosidase inhibitory activities. Out of these extracts and fractions, methanol extracts and polar fractions showed the most

potent bioactivities. The ethyl acetate fractions of the leaf and the stem bark were exhibited significant α-glucosidase activity with the lowest IC_{50} value compared to methanol extracts and other fractions with 4.93 and 5.05 µg/ml, respectively. For DPPH activity, the ethyl acetate fractions has lower value of IC_{50} of 6.39 µg/ml (leaf) and 8.35 µg/ml (stem bark) compared to quercetin (standard) with 8.60 µg/ml. For FRAP, the ethyl acetate fraction (86 mmol Fe (II)/g fraction) of the leaf was the most active than the methanol extracts and other fractions. Methanol extract and hexane fraction of the leaf and stem bark were then subjected to Ultra performance liquid chromatography - mass spectrometer (UHPLC-MS/MS) and gas chromatography mass spectrometry (GC/MS) analyses. The result indicated the identification of 76 metabolites identified through UHPLC-MS/MS, containing phenolics. In addition, 31 compounds have been identified using GC/MS from hexane fractions of *A. pavarii* leaf and 57 compounds from stem bark. The antibacterial activity of methanol extracts and fractions for the leaf and stem bark against MRSA strain using antibacterial assays showed that extracts and fractions of the leaf and stem bark were active with average inhibition zones values ranging from 7.00 to 13.67 mm against the four bacteria. Inhibition zone values as higher as 13.76 mm was obtained with ethyl acetate fraction of the leaf against MRSA ATCC 700699 and MRSA 1 (isolated). Methanol extracts and polar fractions were the most active with MIC values ranging from 0.04 to 2.50 mg/ml against the four bacteria. Ethyl acetate and butanol of the leaf fractions were the most active with MIC values as low as 0.04 mg/ml for the butanol fraction. In bioautography, two of the eight fractions leaf and stem bark fractions had activity with clear zones of inhibition on bioautograms against the purple background. Hexane fractions of the leaf and stem bark were active against all four bacteria and these samples were chosen for further bioassay-guided isolation active compounds by using TLC-bioautographic. Also, ethyl acetate fraction of the leaf was selected for further investigation because (a) it had good antibacterial activity against the four tested bacteria with Inhibition zone value 13.76 mm and its MIC value was as low as 0.08 mg/ml, and (b) as far as our literature survey could ascertain there was no published information on the isolation antimicrobial activity compounds of this plant species. The results revealed the isolation of 15compounds from the leaf and the stem bark. In this study, 4 out of 15 compounds isolated from hexane fractions of leaf and stem bark and ethyl acetate fraction of leaf of different classes showed significant antibacterial activity against MRSA sp and the isolated phenolic compounds did not show any interesting activity. These compounds were lupeol (C4), ursolic acid (C5), betulinic acid (C12) and quercetin 3 - *O* - β glucopyranoside (10). Furthermore, compounds (10) and (12) showed inhibitory activities on desk diffusion assay induced by inhibition zone in MRSA, with inhibition zone values range of 9.00 to 13.00 mm. The lower MIC values were obtained with compound (5) (MRSA1, MRSA2; MIC: 31 µg/ml, MBC: 125 µg/ml) and compound (12) (MRSA2; MIC: 31 µg/ml; MBC: 125 µg/ml).To the best of our knowledge, this study is the first report on the isolation of active compounds from *A. pavarii* and the profiling of metabolites extracted from the stem bark of this plant. The findings of this study may give fundamental data for future research, concerning the medicinal benefit of *A. pavarii*. The isolated bioactive compounds comprising, lupeol, ursolic acid, betulinic acid and quercetin 3-*O*-β glucopyranoside could be used as antibacterial agents against MRSA. Overall, this study revealed the potent antioxidant, α-glucosidase and antibacterial activities of *A. pavarii* and support the future development of active compounds isolated from *A. pavarii* as natural-sourced biological active compounds.

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

AKTIVITI BIOLOGI, ANALISIS FITOKIMIA DAN PENGASINGAN SEBATIAN BIOAKTIF *Arbutus pavarii* Pamp.

Oleh

BUZGAIA NAWAL M BUBAKER

Mei 2020

Pengerusi : Profesor Khozirah binti Shaari, PhD
Institut : Biosains

Produk semula jadi daripada tumbuh-tumbuhan telah digunakan selama berabad-abad untuk merawat dan mencegah pelbagai penyakit. Perkembangan ubat-ubatan kebanyakannya berasaskan produk semula jadi dan pada masa ini para penyelidik memberi tumpuan kepada sumber tumbuh-tumbuhan untuk mengetahui ubat farmaseutikal yang lebih berharga. Berdasarkan data terbaharu daripada organisasi kesihatan dunia (WHO), dua pertiga daripada ubat-ubatan moden berasal daripada tumbuh-tumbuhan. Genus Arbutus (Ericaceae) telah digunakan secara tradisional dalam perubatan rakyat kerana sifat fitoperubatannya, terutamanya Arbutus pavarii. Walau bagaimanapun, tumbuhan terpilih ini masih belum dinilai keberkesanan, kualiti dan konsistensinya untuk menyokong penggunaan tradisionalnya, khususnya dalam merawat diabetes. Walaupun kajian sebelumnya menunjukkan aktiviti biologi A. pavarii sebagai antibakteria, antioksidan dan ejen perencat α-glukosidase, masih terdapat sedikit laporan saintifik mengenai sebatian bioaktif yang menyumbang kepada manfaat kesihatannya.Tujuan utama kajian ini adalah penyelidikan terhadap A. pavarii Pamp sebagai sumber kuat sebatian bioaktif yang bermanfaat. Oleh itu, penyelidikan ini mengfokuskan pada profil dan pengenalpastian metabolit dalam ekstrak metanol dan pecahan-pecahan pelarut daun dan kulit batang untuk menilai potensi mereka bagi aktiviti antimikrob, antioksidan dan α-glukosidase. Untuk mencapainya, beberapa siri protokol pengekstrakan dan pengasingan berpandukan bioassay telah dilakukan. Ekstrak dan pecahan pelarut daun dan kulit batang diuji terhadap Staphylococcus aureus tahan Methicillin (MRSA). Ekstrak-ekstrak telah dipecahkan menggunakan pemecahan cecair-cecair (LLP) untuk mendapatkan pecahan heksana, kloroform, etil asetat, dan butanol. Prosedur pengasingan berpandukan keputusan bioassay, lapisan nipis kromatografi-bioautografi dan resapan cakera telah dilakukan dengan menggunakan teknik kromatografi canggih untuk menulenkan sebatian-sebatian kimia bioaktif. Ekstrak metanol dan pecahan pelarut daun dan kulit batang juga dinilai untuk jumlah kandungan fenolik (TPC), jumlah kandungan flavonoid (TFC), aktiviti pemerangkapan radikal bebas (DPPH), FRAP

dan aktiviti perencatan α-glukosidase. Daripada ekstrak dan pecahan ini, ekstrak metanol dan pecahan polar menunjukkan bioaktiviti yang paling kuat. Pecahan etil asetat daun dan kulit batang menunjukkan aktiviti α-glukosidase yang signifikan dengan nilai IC_{50} terendah berbanding dengan ekstrak metanol dan pecahan lain masing-masing dengan 4.93 dan 5.05 µg/ml. Untuk aktiviti DPPH, pecahan etil asetat mempunyai nilai IC50 yang lebih rendah iaitu 6.39 µg/ml (daun) dan 8.35 µg/ml (kulit batang) berbanding dengan quercetin (standard) dengan 8.60 µg/ml. Untuk FRAP, pecahan etil asetat (86 mmol Fe (II)/g pecahan) daun adalah yang paling aktif berbanding dengan ekstrak metanol dan pecahan lain. Ekstrak metanol dan pecahan heksana dari daun dan kulit batang kemudian dilakukan analisis ultra kromatografi cecair berprestasi tinggi – jisim spektrometri (UHPLC-MS /MS) dan analisis jisim kromatografi gas spektrometri (GC/MS). Hasilnya menunjukkan pengenalan 76 metabolit yang dikenalpasti melalui UHPLC-MS/MS, yang mengandungi fenolik. Selain itu, 31 sebatian telah dikenalpasti menggunakan GC/MS dari pecahan heksana daun A. pavarii dan 57 sebatian dari kulit batang. Aktiviti antibakteria ekstrak dan pecahan metanol untuk kulit daun dan batang terhadap strain MRSA menggunakan ujian antibakteria menunjukkan bahawa ekstrak dan pecahan kulit daun dan batang adalah aktif dengan nilai zon perencatan antara 7.00 hingga 13.67 mm terhadap keempat-empat bakteria. Nilai zon perencatan setinggi 13.76 mm diperolehi daripada pecahan etil asetat daun terhadap MRSA ATCC 700699 dan MRSA 1 (diasingkan). Ekstrak metanol dan pecahan polar adalah yang paling aktif dengan nilai MIC antara 0.04 hingga 2.50 mg/ml terhadap keempat-empat bakteria. Etil asetat dan butanol pecahan daun adalah yang paling aktif dengan nilai MIC serendah 0.04 mg/ml untuk pecahan butanol. Dalam bioautografi, dua daripada lapan pecahan daun dan batang kulit batang mempunyai aktiviti dengan zon perencatan yang jelas pada bioautogram terhadap latar belakang ungu. Pecahan heksana daun dan kulit batang adalah aktif terhadap keempat-empat bakteria dan sampel ini dipilih untuk pengasingan sebatian aktif berpandukan bioassay dengan menggunakan TLC-bioautografi. Begitu juga, pecahan etil asetat daun dipilih untuk penyelidikan selanjutnya kerana (a) ia mempunyai aktiviti antibakteria yang baik terhadap keempat-empat bakteria yang diuji dengan nilai zon perencatan 13.76 mm dan nilai MIC adalah serendah 0.08 mg/ml, dan (b) berdasarkan tinjauan laporan penulisan sebelum ini, kami dapati bahawa tidak ada maklumat yang telah diterbitkan mengenai pengasingan sebatian aktiviti antimikrob dari spesies tumbuhan ini. Hasil kajian ini menunjukkan pengasingan 15 sebatian daripada daun dan kulit batang. Dalam kajian ini, 4 daripada 15 sebatian yang diasingkan daripada pecahan heksana daun dan batang kulit dan pecahan etil asetat daun daripada pelbagai kelas menunjukkan aktiviti antibakteria yang signifikan terhadap MRSA sp dan sebatian fenolik yang diasingkan tidak menunjukkan aktiviti yang menarik. Sebatian ini adalah lupeol (C4), asid ursolic (C5), asid betulinic (C12) dan quercetin 3 - *O* - β glucopyranoside (10). Tambahan pula, sebatian (10) dan (12) menunjukkan aktiviti perencatan pada ujian resapan cakera yang disebabkan oleh zon perencatan di MRSA, dengan nilai zon perencatan dalam linkungan antara 9.00 hingga 13.00 mm. Nilai MIC yang lebih rendah diperolehi daripada sebatian (5) (MRSA1, MRSA2; MIC: 31 µg/ml, MBC: 125 µg/ml) dan sebatian (12) (MRSA2; MIC: 31 µg/ml; MBC: 125 µg/ml). Sepengetahuan kami, kajian ini adalah laporan pertama mengenai pengasingan sebatian aktif dari A. pavarii dan profil metabolit yang diekstrak daripada kulit batang tumbuhan ini. Penemuan kajian ini dapat memberikan asas data untuk penyelidikan masa depan, mengenai manfaat perubatan A. pavarii. Sebatian bioaktif yanf diasingkan terdiri daripada,

lupeol, asid ursolic, asid betulinik dan quercetin 3-*O*-β glukopranosida dapat digunakan sebagai agen antibakteria terhadap MRSA. Secara keseluruhannya, kajian ini mendedahkan aktiviti antioksidan, α-glukosidase dan antibakteria A. pavarii yang kuat dan menyokong perkembangan sebatian aktif pada masa depan yang diasingkan dari A. pavarii sebagai sebatian aktif biologi berasaskan sumber semula jadi.

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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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Date: 06 May 2021

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This is to confirm that:

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Signature: _____
Name of Member of Supervisory Committee: Associate Professor Dr. Yaya Rukayadi

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LIST OF ABBREVIATIONS

ANOVA	Analysis of Variance
ATCC	American Type Culture Collection
Br	Broad
n- BuOH	n-Butanol
β	Beta
CC	Column Chromatography
$CDCl_3$	Deuterated Chloroform
CFU	Colony Forming Unit
$CHCl_3$	Chloroform
CHX	Chlorohexidine
CLSI	Clinical Laboratory Standard Institute
COSY	Correlations Spectroscopy
CPC	Centrifugal Partition Chromatography
d	Doublet
dd	Doublet of doublet
DEPT	Distortionless Enhancement by Polarization Transfer
1D-NMR	One-Dimensional Nuclear Magnetic Resonance Spectroscopy
2D-NMR	Two-Dimensional Nuclear Magnetic Resonance Spectroscopy
DMSO	Dimethyl sulfoxide
DMSO-d_6	Deuterated Dimethyl sulfoxide
DPPH	Diphenyl picrylhdrazyl
DW	Dry Weight
EtOAc	Ethyl acetate
FRAP	Ferric Reducing Antioxidant Power Assay
FIC	Fractional Inhibitory Concentration
g	Gram

GAE	Gallic Acid Equivalent
GC-MS	Gas Chromatography- Mass Spectrometry
^{1}H-NMR	Proton Nuclear Magnetic Resonance Spectroscopy
HMBC	Heteronuclear Multiple-bond Correlation
HPLC	High Performance Liquid Chromatography
HPLC-DAD-ESI-MS/MS	High-Performance Liquid Chromatography-Diode Array Detector-Hyphenated with Tandem Mass Spectrometry
HSQC	Heteronuclear Single-quantum Correlation
Hz	Hertz
IC_{50} / EC_{50}	Inhibition Concentration at 50 percent
IR	Infrared Spectroscopy
IZD	Inhibition Zone Diameter
J	Coupling constant in Hz
KCCM	Korean Culture Centre of Microorganisms
l	Litre
LC-MS	Liquid Chromatography–Mass Spectrometry
LC-UV	Liquid Chromatography- Ultraviolet
m	Multiple
MBC	Minimal Bactericidal Concentration
m.p.	Melting point
µg	Microliter
µL	Microliter
m/z	Mass per Charge
CD_3OD	Methanol-d_4
CH_3OH-d_4	Deuterated Methanol-*d4*
MHA	Mueller Hinton Agar
MHB	Mueller Hinton Broth
MeOH	Methanol

mHz	MegaHertz
MIC	Minimal Inhibitory Concentration
ml	Milliliter
mm	Millimeter
MS	Mass Spectrometry
MS/MS	Mass / Mass Spectrometry
MTT	3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl tetrazolium bromide
MRSA	Methicillin-resistant *Staphylococcus aureus*
NMR	Nuclear magnetic resonance spectroscopy
ppm	Part per million
PBS	Phosphate Buffered Saline
PNPG	p-Nitrophenyl-α-D-glucopyranoside.
QE	Quercetin Equivalents
RIZD	Relative Inhibition Zone Diameter
s	Singlet
t	Triplet
TLC	Thin Layer Chromatography
TPC	Total Phenolic Contents
TPTZ	(2,4,6-tri(2-pyridyl)-s-triazine)
Rt	Retention Time
UV/VIS	Ultravoilet/visible
δ	Chemical Shift in ppm
WHO	World health organization
ZI	Zone of Inhibition

LIST OF SCHEMES

CHAPTER I

INTRODUCTION

1.1 Background

Traditional medicine using crude extracts or mixtures of chemical compounds have been used by many populations as a treatment of various diseases over the years. It is important to screen the plant phytochemicals that have medicinal uses for biological activities. This provides a platform for isolation and identification of biologically active compounds. Besides, the world has been experiencing issues with the resistivity of certain antimicrobial agents against a variety of pathogenic microbes due to the extensive use of various antibiotics. Methicillin-resistant *Staphylococcus aureus* (MRSA) is an important pathogenic organism, which can be found in various parts of the world including the U.S, China, India, and Malaysia (Ong et al., 2017). The orthodox antibiotics treatment method to for MRSA control was not adequate to efficiently reduce the occurrence of MRSA in the regions that are susceptible to the infection. Thus, a need to produce an antibiotic from natural resources including therapeutic extracts of plant to improve the efficiency and effectiveness of orthodox antibiotics could never be overemphasized (Abreu et al., 2017). On the contrary, oxidation procedures are the important tools for free radical generation in the course of metabolism of food substances, chemicals, and others biosystems. Generated reactive oxygen (ROS) or nitrogen (RNS) species are neutralized by the action of human enzymes including catalase, and hydroperoxidase that convert hydrogen peroxide, and hydroperoxides to non-radical forms (Diamanti-Kandarakis et al., 2017).

On the other hand, the interest of exploring natural sources of antioxidants is on the rise, demonstrating their higher potency, and lower toxicity compared to synthetic drugs (Han et al., 2018). A number of plant species have been used as drug throughout the world due to the presence of phytochemicals in their extracts, having high antioxidant activities (Afsheen et al., 2018). Owing to the structural variation of secondary metabolites in medicinal plants, the plants provide wide range of natural antioxidants. Currently, the medicinal plants have been fully recognized as a source of natural antioxidant agents, including phenolic, and aromatic compounds (Chand et al.,2017). Other than that, this study attempted to screen the α-glucosidase inhibitory activity of the selected plant. A number of synthetic α-glucosidase inhibitors, including metformin and acarbose are available in the market to treat diabetes mellitus DM, fulfilling the desires of diabetic patients with some side effects (Chidambaram et al.,2019). Recent studies have shown the efficiency of some herbal drugs with remarkable effectiveness. Therefore, there is a need to find natural-based drugs plants that contain a substantial amount of α-glucosidase inhibitors compounds. (Chidambaram et al.,2019).

The *Arbutus* (Ericaceae) is one of the largest genera, which has significant medicinal properties and used in the treatment of many serious diseases. Based on previous records, various *Arbutus* species are known for its laxative, cardiovascular, antitumor, anti-hypertensive, antimicrobial antioxidant, antidiabetic, and antibacterial activities. The key chemical constituents identified in the leaf of *Arbutus* species are phenols, triterpenes, and essential oils (Tenuta et al.,2019). Similarly, the qualitative phytochemical analysis displayed the presence of cardiac glycosides, polyphenols, flavonoids, triterpenes, tannins, sugars, and sterols in leaf and fruits of *A. pavarii* (Alghazeeret al., 2016; Tenuta et al.,2019).

Arbutus pavarri has been used by ancient traditional herbalists for the treatment of gastritis, various kinds of ailments, and infectious diseases such as renal infections (El-Darier & El-Mogaspi, 2009). According to Abouzeed et al, (2013), *A. pavarri* plant is very popular in Libya, having inadequate studies on its bioactivities and chemical composition. Similarly, the bioactive compounds in *A. pavarri* plant were not extensively reported, and their effect on microorganisms was not comprehensively studied. Due to the above-mentioned reasons, this study is the first of its kind to extract and screen the antibacterial, antioxidant, and α-glucosidase inhibitory activities, and isolate, characterize, identify anti-MRSA compounds from the leaf and stem bark.

1.2 Problem Statement

Since ancient times, plant extracts have been used for conventional diabetes therapy, microbial infections, stress-related illness, and antioxidant sources. They are now generally accepted as supplementary substitutes for orthodox medicines. Plant Phytochemicals can cause membrane destruction, complicate the cell wall, inactivate enzymes and cause substrate deprivation, as well as they prevent oxidative modification by neutralizing free radicals, scavenging oxygen or decomposing peroxides by their antioxidant activity. However, not all the phytochemicals that have therapeutic applications for biological activities are screened. Since several skin disorders are associated with inflammation and the release of free radicals, leading to oxidative and cellular damage and bacterial infections, the presence of antioxidants and antimicrobials can explain the effectiveness of plants in the treatment of skin infections. Accordingly, new natural antioxidant molecules in medicinal plants warrant further investigation for the function that they may play in the prevention of diseases, such as diabetes by battling oxidative stress and its related pathologies.

It has been shown that the available synthetic antioxidants and antimicrobials have harmful side effects. Therefore, plants can be more effective, less toxic, and cost-effective antioxidants and antimicrobials from natural sources. Endemic plants can also be a source of new active ingredients for combating antibiotic resistance. In addition, most of the used drugs become unworkable due to the resistance of bacteria. Consequently, the hunt for new active molecules with a wide spectrum of action has become a requirement in the face of the emergence of resistant types of certain bacteria against some antibiotics. One strategy for this research was to investigate active

compounds in *A. pavarii* used in conventional medicines, which have been long used to counter oxidation stress, diabetes and bacterial infections.

1.3 The Hypothesis

Some scientific studies showed that many *Arbutus* species have potent antioxidant, anti-diabetes, antibacterial activities against MRSA. Based on these observations, it was reasonable to assume that *Arbutus* species traditionally used for the treatment of cancer, diabetes and bacterial infections may contain bioactive compounds, which can be scientifically identified and isolated for the treatment of diabetes and bacterial resistance infection. Hence, *A. pavarii* might possess these activities. The approach was first to screen the antioxidant activity, alpha-glucosidase inhibition and antibacterial assay against species closely similar to resistant antibiotics (MRSA). It is hoped that potential bioactive compounds can be identified and purified and theses possible drugs would be tested against MRSA.

1.4 Aim and Objectives of the Study

The main aim of the current research is to identify the therapeutic effectiveness of *A. pavarii* by conducting the antimicrobial, antioxidant and α-glucosidase inhibitory activity assays. Moreover, this research focussed on the evaluation of antibactrial activities of the isolated compounds from leaf and stem bark fractions of *A. pavarii*.

1.5 This study embarks on the following objectives

1- To screen the total phenolic contant, total flavonoids contant, antioxidant properties and α-glucosidase inhibitory activity of the crude extracts, and fractions of the leaf and bark of *A. pavarii.*
2- To profile the phytochemical composition of the methanol extracts and hexane fractions of the leaf and stem bark using high-performance liquid chromatographywith tandem mass spectrometry (UHPLC-ESI-MS/MS) and gas chromatography-mass spectrometry (GC-MS).
3- To determination the highes antibacterial activity of the leaf and the stem bark fractions against Methicillin-resistant *S. aureus* (MRSA).
4- To isolate and purify of the compounds responsible for *A.pavarri*‘s ati-MRSA employing combinations of various chromatographic methods (CC, CPC, preparative TLC, and HPLC).Also, to elucidate the structures of the isolated compounds using various spectroscopic techniques; (IR), (NMR) and (MS)
5- To evaluate bioactivity of the bioactive compounds by disk diffusion, MIC and MBC.

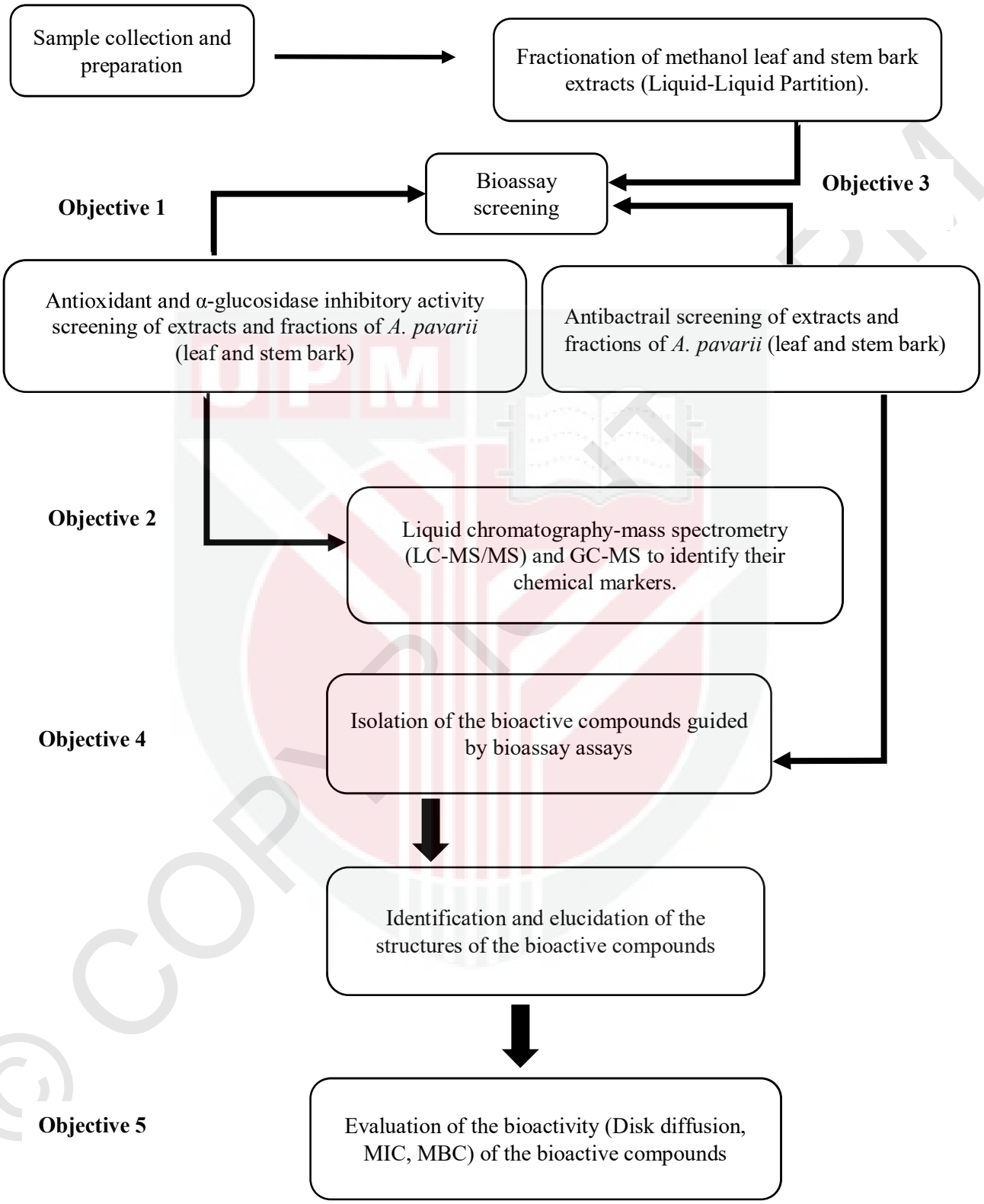

Figure 1.1 : Outlines of the study

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