CHEMICAL CONSTITUENTS AND BIOACTIVITIES OF *Artocarpus scortechinii* KING. AND *A. hispidus* F.M. JARRETT

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Specially dedicated to my beloved family,

My husband & my sons,
Mohd Hasrul Ishak
Muhammad Hadid Zikry Mohd Hasrul
Muhammad Zayd Zikry Mohd Hasrul

My parents and parents in law,
Mohd Arriffin Samsuddin & Zainun Wan Omar
Ishak Sulaiman & Hamidah Johar

My siblings and sister in law,
Norzafriza Mohd Arriffin
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For their love, concern, encouragement and continuous prayer for my success in completing this research
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ABSTRACT

Two *Artocarpus* species from Malaysia, namely *A. scortechinii* King and *A. hispidus* F.M. Jarrett were investigated. The aims of this study were to isolate and identify the phytochemicals from different parts of these two species and also to evaluate the biological activities of the crude extracts and isolated compounds using antioxidant, α-glucosidase and anti-tyrosinase inhibition assays. Cold extractions were performed using *n*-hexane, dichloromethane, ethyl acetate and methanol on the stem barks and leaves of *A. scortechinii* to obtain the respective extracts. Extractions of *A. hispidus* were carried using *n*-hexane, dichloromethane and methanol. Fifteen compounds were isolated from these two *Artocarpus* species. Two new compounds together with thirteen known compounds were identified spectroscopically and by comparison with literature data. New compounds were isolated from the leaves of *A. scortechinii* and identified as (2*R*,3*R*)-5-hydroxy-6,7-(2,2-dimethylpyrano)-2,3-dihydroflavonol and (*2R,3R*)-7-hydroxy-5-methoxy-8-prenyl-2,3-dihydroflavonol together with macakurzin C, flemichapparin A, β-sitosterol, apigenin and luteolin. 4',5-Dihydroxy-6,7-(2,2-dimethylpyrano)-2'-methoxy-8-γ,γ-dimethylallyflavone, stigmasterol, cudraflavone A, artocarpin, cycloartobiloxanthone, artonin E, oxyresveratrol and engelitin were obtained from the stem barks of *A. scortechinii*. Purification of the extracts of *A. hispidus* afforded four known compounds and identified spectroscopically as 4',5-dihydroxy-6,7-(2,2-dimethylpyrano)-2'-methoxy-8-γ,γ-dimethylallyflavone, stigmasterol, artocarpin and oxyresveratrol. Extracts from these two *Artocarpus* species were screened for total phenolic contents using Folin Ciocalteau's reagent. Among all extracts tested, methanol extract of the stem barks of *A. hispidus* showed the highest phenolic content with TPC value of 218.93 mg GAE/g dw followed by methanol extract of the stem barks of *A. scortechinii* with TPC value of 136.84 mg GAE/g dw. The methanol extract of the stem barks of *A. hispidus* also showed the highest scavenging action among all the extracts with an IC_{50} value of 28.2 µg/mL towards DPPH radical. Luteolin displayed the best radical scavenging activity compared to other isolated compounds towards DPPH and ABTS radical with IC_{50} values of 9.51 µg/mL and 124.4 µg/mL, respectively. Luteolin also displayed the highest FRAP equivalent value of 4.07 ± 0.18 mM, which may act as good reducing agent. In α-glucosidase inhibition assay, oxyresveratrol was noticeably having strongest inhibition with an IC_{50} value of 3.88 µM. The methanol extract of stem barks of *A. hispidus* displayed the highest percentage inhibition (88.2%) in anti-tyrosinase inhibition activity followed by methanol extract of *A. scortechinii* (86.7%). Among the isolated compounds, oxyresveratrol exhibited the most potent tyrosinase inhibitory activity (92.3%) higher than the positive control, kojic acid (85.5%).

ABSTRAK

Dua spesies *Artocarpus* Malaysia, iaitu *A. scortechinii* King dan *A. hispidus* F.M. Jarrett telah dikaji. Tujuan kajian ini ialah untuk mengasingkan dan mengenalpasti fitokimia daripada bahagian berbeza dua spesies ini dan juga menilai aktiviti biologi ekstrak mentah dan sebatian terpencil menggunakan pengujian antioksidan, α-glukosidase dan perencatan anti-tirosinase. Pengekstrakan sejuk telah dilakukan menggunakan *n*-heksana, diklorometana, etil asetat, dan metanol ke atas kulit batang dan daun *A. scortechinii* untuk mendapatkan ekstrak masing-masing. Pengekstrakan *A. hispidus* telah dijalankan menggunakan *n*-heksana, diklorometana dan metanol. Lima belas sebatian telah dipencilkan daripada dua spesies *Artocarpus* tersebut. Dua sebatian baharu bersama-sama tiga belas sebatian yang diketahui telah dikenalpasti melalui spektroskopi dan perbandingan dengan data dari literatur. Sebatian baharu telah dipisahkan daripada daun *A. scortechinii* dan dikenalpasti sebagai (*2R,3R*)-5-hidroksi-6,7-(2,2-dimetilpirano)-2,3-dihidroflavonol dan (*2R,3R*)-7-hidroksi-5-metoksi-8-prenil-2,3-dihidroflavonol, bersama-sama dengan macakurzin C, flemichapparin A, β-sitosterol, apigenin dan luteolin. 4',5-Dihidroksi-6,7-(2,2-dimetilpirano)-2'-metoksi-8-γ,γ-dimetilallilflavon, stigmasterol, cudraflavon A, artokarpin, silkoartobiloxanton, artonin E, oksiresveratrol dan engelitin telah diperolehi daripada kulit batang *A. scortechinii*. Penulenan ekstrak *A. hispidus* telah menghasilkan empat sebatian yang diketahui dan dikenalpasti secara spektroskopi sebagai 4',5-dihidroksi-6,7-(2,2-dimetilpirano)-2'-metoksi-8-γ,γ-dimetilallilflavon, stigmasterol, artokarpin dan oksiresveratrol. Ekstrak daripada dua spesies *Artocarpus* tersebut telah disaring untuk jumlah kandungan fenolik menggunakan reagen Folin Ciocalteau. Antara ekstrak yang diuji, ekstrak metanol kulit batang *A. hispidus* menunjukkan kandungan fenolik yang tertinggi dengan nilai TPC 218.93 mg GAE/g dw diikuti oleh ekstrak metanol kulit batang *A. scortechinii* dengan nilai TPC 136.84 mg GAE/g dw. Ekstrak metanol kulit batang *A. hispidus* juga menunjukkan pemerangkapan tertinggi antara semua ekstrak dengan nilai IC_{50} 28.2 µg/mL terhadap radikal DPPH. Luteolin memaparkan aktiviti pemerangkapan radikal terbaik berbanding sebatian terpencil yang lain terhadap radikal DPPH dan ABTS dengan nilai IC_{50} 9.51 µg/mL dan 124.4 µg/mL masing-masing. Luteolin juga memaparkan nilai setara FRAP yang tertinggi, iaitu 4.07 ± 0.18 mM, yang mungkin boleh bertindak sebagai agen penurunan yang baik. Dalam pengujian rencatan α-glukosidase, oksiresveratrol didapati mempunyai perencatan tertinggi dengan IC_{50} 3.88 µM. Ekstrak metanol kulit batang *A. hispidus* memaparkan peratus perencatan tertinggi (88.2%), dalam akiviti rencatan anti-tirosinase diikuti ekstrak metanol *A. scortechinii* (86.7%). Antara sebatian terpencil, oksiresveratrol mempamerkan potensi merencat aktiviti tirosinase tertinggi (92.3%), lebih tinggi daripada kawalan positif, asid kojik (85.5%).

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α	-	Alpha
β	-	Beta
δ	-	Chemical shift
δ_H	-	Chemical shift for proton
δ_C	-	Chemical shift for carbon
AA	-	Ascorbic acid
Abs	-	Absorbance
ABTS	-	2,2'-azinobis (3-ethyl-benzothiazoline-6-sulfonic acid)
APCIMS	-	Atmospheric Pressure Chemical Ionization Mass Spectrometry
ATR	-	Attenuated Total Reflection
BHA	-	Butylated hydroxyanisole
BHT	-	Butylated hydroxytoluene
Br	-	Broad
^{13}C NMR	-	Carbon Nuclear Magnetic Resonance
Calcd.	-	Calculated
CC	-	Column Chromatography
cm^{-1}	-	per centimeter
COSY	-	Correlation Spectroscopy
1D	-	1 Dimension
2D	-	2 Dimension
d	-	Doublet
dd	-	Doublet of Doublets
DEPT	-	Distortionless Enhancement by Polarization Transfer
DMSO	-	Dimethyl sulfoxide
DPPH	-	2,2'-Diphenyl-1-picrylhydrazyl
EIMS	-	Electron Impact Mass Spectrometry

EtOAc	-	Ethyl acetate
FRAP	-	Ferric reducing antioxidant potential
g	-	Gram
GC-MS	-	Gas Chromatography-Mass Spectrometry
^{1}H NMR	-	Proton Nuclear Magnetic Resonance
HMBC	-	Heteronuclear Multiple Bond Correlation
HMQC	-	Heteronuclear Multiple Quantum Coherence
HRAPCIMS	-	High Resolution Atmospheric Pressure Chemical Ionization Mass Spectrometry
Hz	-	Hertz
I%	-	Percent Inhibition
IC_{50}	-	Inhibition Concentration at 50%
int.	-	Intensity
IR	-	Infrared
J	-	Coupling constant
kg	-	Kilogram
lit.	-	Literature
L-DOPA	-	L-tyrosinase-3,4-dihydroxyl-L-phenylalanine
m	-	Multiplet
m/z	-	Mass to charge
M^{+}	-	Molecular ion
MHz	-	Megahertz
mg	-	Milligram
mL	-	Milliliter
mM	-	Milimolar
mp	-	Melting point
MS	-	Mass Spectrometry
µL	-	Microliter
µm	-	Micrometer
µM	-	Micromolar
NMR	-	Nuclear Magnetic Resonance
ppm	-	Parts per million
PTLC	-	Preparative Thin Layer Chromatography
Ref	-	Reference

rel.	-	Relative
R_f	-	Retention factor
s	-	Singlet
sh	-	Shoulder
t	-	Triplet
TLC	-	Thin Layer Chromatography
TPTZ	-	2,4,6-tripyridyl-s-triazine
Trolox	-	6-Hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid
UV	-	Ultraviolet
VLC	-	Vacuum Liquid Chromatography

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CHAPTER 1

INTRODUCTION

1.1 General Introduction

Plants had been used for medicinal purposes by local practitioners since thousands of years ago in whole world and still been used until today. Plants contain thousands valuable treasures that need to be explored. Plants can served as main source of natural product research in discovery of biologically active new drugs [1-3]. Chemical investigations can lead to new findings that can be used in the future by people to heal various illnesses. Nowadays people are exposing to various type of diseases such as HIV/AIDS, Alzheimer, malaria, and cancer which can threat life. Discovery of new medicines and antibiotics are important to treat these serious diseases. High demand on the new generation of antibiotics and medicines had led to more phytochemical study from natural plants. Moreover, about 80% of the population in the world according to The World Health Organization were using plants as traditional medicines [2].

Recently, people prefer using plants origin than chemicals as the source in drug discovery due to safety and less cost. Plants can be serving as important raw materials for production of new medicines because there are many evidences showed that the plant extracts may possess several useful biological activities including antibacterial, antitubercular, antiviral, antifungal, antiplatelet, anti-tyrosinase inhibitory and cytotoxic activities [4]. The discovery of the drug from plants also can depend on the bioassay

guided isolation methods to conduct the isolation of the important and desire drugs [5-6]. This method can lead to isolation of the active compounds.

To date, less than 10% of the world's biodiversity had been explored on the phytochemical and active compounds in plants. Many more discoveries await to be investigated and disinterred for the use of the future [7]. Plants have been used as source of drug discovery for thousands of years. Isolation of the active compounds from plant involves numerous fields and various methods of analysis. It begins with a botanist, ethnobotanist or plant ecologist who identifies the plant of interest. Phytochemist (Natural product chemist) will prepare the extract and conduct the process of isolation. The compounds will be elucidated and appropriate screening assay will be done on the target compounds. Pharmacologist will take further action for the drug discovery [8].

Malaysia is strategically located in the equator with the balance of hot and wet climate that make our country having wide range of plants species. Due to this reason, Malaysia's forests are rich with varieties of plant species that are valuable and suitable for the medicine discovery. Moraceae is one of the plant families that have potential to be explored due to widely used in various traditional medicines [4, 10-12].

1.2 Moraceae Family

Moraceae family is also known as the mulberry family. It comprises of 60 genera and over 1400 species distributed worldwide. Plants of this family are most abundant and ecologically important in tropical rainforest. These plants are usually trees, shrubs or climbers which produce white latex. Moraceae plants are closely related to Ulmaceae and Urticaceae plants except Moraceae plants have latex [9]. Three main genera in Moraceae family are *Ficus, Morus* and *Artocarpus*. Several of the genera produce timber and edible.

1.3 Genus *Artocarpus*

Genus *Artocarpus* consists of about 50 species which are widely distributed over tropical rain-forests. *Artocarpus* are known for their edible fruits such as *A. heterophyllus* (jackfruit), *A. altilis* (breadfruit) and *A. integer* (cempedak). This genus had been well known to contain rich sources of prenylated flavonoids, terpenoids, stilbenoids and xanthones [10-13]. More interestingly, they had been reported widely as traditional folk medicine for the treatment of malaria fever, liver cirrhosis, hypertension and diabetes [14-17]. Almost whole parts of this species had its own benefit on human for medicinal purposes. The root can cure asthma and fever, the seed can relieve the diarrhea, the wood act as sedative, the leaves act as antisyphilitic in human and relieve ulcer while the leaf ash can cure wounds. [9]. **Table 1.1** shows several *Artocarpus* species in Malaysia, their common names and the distributions.

Table 1.1: Several *Artocarpus* species in Malaysia

Species	Common Name	Distributions
A. anisophyllus	Keledang babi	Rare species in lowland forest such as Johor and Negeri Sembilan.
A. altilis	Breadfruit	Frequent in the village in Malaysia.
A. chempeden	Cempedak	Cultivated throughout Malaysia.
A. communis	Sukun	Frequent in the village in Malaysia.
A. dadah	Tampang bulu	Lowland forest throughout Malaysia.
A. elasticus	Terap nasi	Lowland forest throughout Malaysia.
A. fulvicortex	Tampang gajah	Scattered throughout Malaysia in lowland forest.
A. gomenzianus	Tampang burung	Rare species in lowland forest such as Kedah, Kelantan, Pahang, Negeri Sembilan and Johor.
A. heterophyllus	Nangka	Cultivated throughout Malaysia.
A. hispidus	Temponek	Lowland forest such as Pulau Pinang, Perak, Pahang, Terengganu and Selangor.
A. integer	Cempedak	Cultivated throughout Malaysia.
A. integer var silvestris	Bangkong	Widely distributed in Malaysia from the lowland to mountain forest.
A. kemando	Pudu	Lowland forest including swamps such as Terengganu, Pahang and Selangor.
A. lanceifolius	Keledang	Lowland and hill forest throughout

		Malaysia.
A. lowii	Miku	Rare species in Malaysia and found in lowland forest.
A. scortechinii	Terap hitam	Rare species in lowland forest in Malaysia.
A. teysmanii	-	Rare species in swampy habitat in Perak and Selangor.

1.3.1 *A. scortechinii* King.

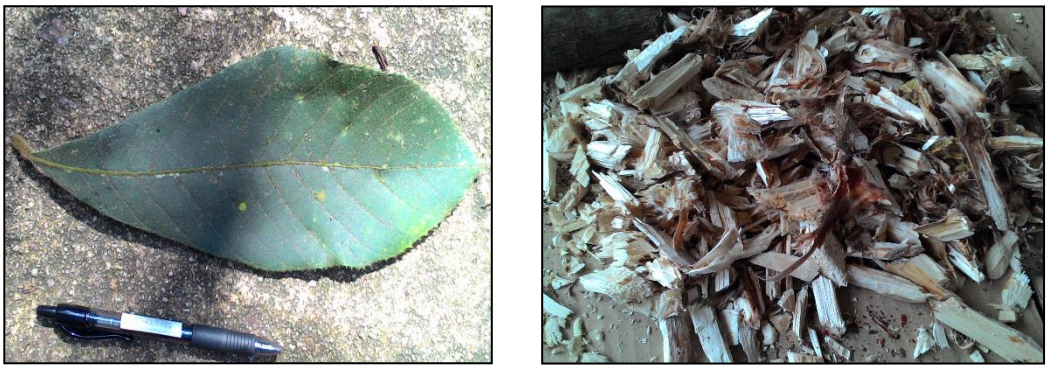
A. scortechinii King. (**Figure 1.1**) is locally known as *terap hitam*. It can be found in lowland forest of Malaysia and Sumatra, Indonesia [9]. This species had been identified to be similar to *A. elasticus* ("terap nasi"). The difference with *A. elasticus* is on the stem which is darker while the leaves are not too large and wide.

(**a**) (**b**)

Figure 1.1: (**a**) Leaves and (**b**) stem barks of *A. scortechinii* King.

1.3.2 *A. hispidus* F.M. Jarrett

A. hispidus F.M. Jarrett (**Figure 1.2**) is an evergreen tree commonly known as "temponek". The tree can reach 20 m tall with the girth of 120 cm. This plant can be found in lowland forest of Pulau Pinang, Perak, Pahang, Terengganu and Selangor. This species had been identified to have similarity with *A. rigidus*. The leaves of *A. hispidus* are densely hairy with stalks about 1-2 cm long [8].



(a) **(b)**

Figure 1.2: (**a**) Leaves and (**b**) stem barks of *A. hispidus* F.M. Jarrett

1.4 Problem Statements

Artocarpus species have been proven as rich source of phenolic compounds especially flavonoids based on many previous reports. However, not all species had been scientifically studied for their phytochemicals and bioactivities. Previous studies on *A. scortechiniii* were only on the barks which were collected from different location in Malaysia [18-19]. Another study had been carried out by Indonesian researchers on the heartwood [20]. The leaves and stem barks of *A. scortechinii* had not been investigated yet. Thus, the investigation on the presence of secondary metabolites from this species is important since there is still insufficient information regarding the chemical constituents in leaves and stem barks part. The samples were collected from Bukit Fraser, Pahang. Different locality of the sample may result in the isolation of different chemical compounds and bioactivities. To date, no research had been done on *A. hispidus.* A thorough literature search did not found any report on the phytochemical and isolation work of *A. hispidus* thus far. Therefore, extensive studies are needed to provide the data of the chemical compounds present in these two rare species of *Artocarpus.*

1.5 Research Objectives

The objectives of this research are:

i) To isolate the chemical constituents from the stem barks and leaves of *A. scortechinii* King. and *A. hispidus* F.M. Jarrett.

ii) To elucidate the structure of pure compounds using spectroscopic methods (FTIR, UV, MS and NMR)

iii) To evaluate the ability of the extracts and pure compounds on antioxidant, α-glucosidase and anti-tyrosinase inhibition activities.

1.6 Significant of Study

Plants had been well documented for their medical uses and treatments of numerous diseases. In recent years, the awareness of the researchers to explore on the natural based product is increasing. The aim was to give evidence and supported data on the medicinal uses originated from plants. Phytochemical screening and isolation of these two species (*A. scortechinii and A. hispidus*) could be used as alternative source of bioactive compounds for further research. The isolation of the pure bioactive compounds could also lead to scientific proof of their medicinal properties and give additional knowledge for pharmaceutical field.

1.7 Scope of Study

These studies focused on the phytochemicals and bioactivities of two Malaysia's rare *Artocarpus* species i.e. *A. scortechinii* and *A. hispidus*. The parts of the plant investigated are the stem barks and leaves. The dried samples were soak successively using solvents with different polarity to give the extracts. All extracts were fractionated

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