PHYTOCHEMICALS AND BIOACTIVITIES OF *ARTOCARPUS LANCEIFOLIUS* ROXB AND *ARTOCARPUS MAINGAYI* KING

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PHYTOCHEMICALS AND BIOACTIVITIES OF *ARTOCARPUS LANCEIFOLIUS* ROXB AND *ARTOCARPUS MAINGAYI* KING

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Dedicated to

My beloved parents

My sisters and brother

My friends.

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PREFACE

This thesis is the resulted of my own work carried out in the Department of Chemistry, Faculty of Science, Universiti Teknologi Malaysia between June 2008 and July 2010 under the supervision of Dr. Shajarahtunnur Jamil. Part of my work describe in this thesis has been reported in the following publications:

1. Noor Safina Sulaiman and Shajarahtunnur Jamil (2009). "Screening of *Artocarpus lanceifolius* for Antibacterial Activity". Second International Conference and Workshops & Regional Fundamental Science Seminar 2009, 2-4 June 2009, Johor Bahru, Malaysia, **1**, 242-244, ISBN : 978-983-9805-73-4

2. Noor Safina Sulaiman, Shajarahtunnur Jamil (2009). "Phytochemicals Studies and Antimicrobial Activities of *Artocarpus lanceifolius*". 2nd Junior Chemist Colloqium 2009, 1-2 July 2009, UNIMAS Sarawak, Malaysia.

ABSTRACT

Phytochemical studies on *Artocarpus lanceifolius* Roxb. and*Artocarpus maingayi* King have successfully isolated seven flavonoids and two plant sterols. Five compounds were successfully isolated from the stem bark of *Artocarpus lanceifolius* which were identified as 9,19-cyclolanost-24-en-3-acetate, cycloartobiloxanthone, artonol B, 7,8-(2,2-dimethylchromeno)-10-(2-hydroxyl-1-methylethyl)-2',4',5',5-tetrahydroxyflavone, and artonin E. Two flavans which were tentatively elucidated as 7,8-(2,2-dimethylchromano)-4',4,5-trihydroxy-2'-methoxyflavan and 8-(11-methyl-11-butenyl)-3,4',5,7-tetrahydroxy-2'-methoxyflavan have been isolated from the leaves of *Artocarpus lanceifolius*. Another two compounds were isolated from the leaves of *Artocarpus maingayi* which were identified as carpachromene, and β-sitosterol. Structures of all compounds were elucidated spectroscopically by Nuclear Magnetic Resonance, Infrared, Ultraviolet Spectroscopies and Mass Spectrometry. Biological activities were carried out on the crude extracts and pure compounds. The antimicrobial testing on the crude extracts and pure compounds were carried out against the Gram-positive bacteria, *Bacillus subtilis* and *Staphylococcus aureus* and Gram-negative bacteria, *Escherichia coli* and *Pseudomonas aeruginosa*. Most of the crude extracts and pure compounds showed significant antimicrobial activity. A pure compound, 7,8-(2, 2-Dimethylchromeno)-10-(2-hydroxyl-1-methylethyl)-2',4',5',5-tetrahydroxyflavone showed most significant antimicrobial activity compared to other isolated compounds and crude extracts with the minimum bactericidal concentration and minimum inhibition concentration value between 31.25 – 62.5 µg/mL. The antioxidant test on the crude extracts and pure compounds from both plant species showed potential free radical scavenger against 2,2-diphenyl-1-picrylhydrazyl. Artonin E exhibited the strongest antioxidant activity with 50% scavenging concentration at 46.9 µg/mL while the ethyl acetate crude extract from the stem bark of *Artocarpus maingayi* showed 50% scavenging concentration at 60.1 µg/mL.

ABSTRAK

Kajian fitokimia ke atas *Artocarpus lanceifolius* Roxb. dan *Artocarpus maingayi* King berjaya mengasingkan tujuh sebatian flavonoid dan dua sebatian sterol tumbuhan. Lima sebatian telah berjaya diasingkan daripada kulit batang *Artocarpus lanceifolius* yang di kenalpasti sebagai 9,19-siklolanos-24-en-3-asetat, sikloartobiloxanton, artonol B, 7,8-(2,2-dimetilkromeno)-10-(2-hidroksil-1-metiletil)-2',4',5',5-tetrahidroksiflavon, dan artonin E. Dua flavan yang dinamakan sebagai 7,8-(2,2-dimetilkromano)-4',4,5-trihidroksi-2'-metoksiflavan dan 8-(11-metil-11-butenil)-3,4',5,7-tetrahidroksi-2'-metoksiflavan telah diasingkan daripada daun *Artocarpus lanceifolius*. Dua lagi sebatian kimia telah diasingkan daripada daun *Artocarpus maingayi* yang dikenalpasti sebagai karpakromen dan *β*-sitosterol. Struktur semua sebatian kimia ini dikenalpasti berdasarkan kepada kajian spektroskopi resonans magnet nukleus, infra merah, spektroskopi ultralembayung dan spektrometri jisim. Kajian aktiviti biologi telah dijalankan ke atas ekstrak mentah dan sebatian tulen. Ujian antibakteria ke atas ekstrak mentah dan sebatian tulen telah dijalankan dengan menggunakan Gram positif, *Bacillus subtilis* dan *Staphylococcus aureus* manakala Gram-negatif, *Escherichia coli* dan *Pseudomonas aeruginosa.* Kebanyakan ekstrak mentah dan sebatian tulen menunjukkan aktiviti antibakteria yang signifikan. Satu sebatian tulen, 7,8-(2,2-dimetilkromeno)-10-(2-hidroksil-1-metiletil)-2',4',5',5-tetrahidroksiflavon menunjukkan aktiviti antibakteria yang paling signifikan berbanding dengan sebatian tulen yang lain dengan nilai kepekatan minimum bakterisidal dan kepekatan minimum perencatan di antara 31.25 hingga 62.5 μg/mL. Ujian antioksidan ke atas ekstrak mentah dan sebatian tulen dari kedua-dua spesies *Artocarpus* menunjukkan keupayaan untuk bertindak sebagai perencat radikal bebas terhadap 2,2-difenil-1-picrylhidrazil. Artonin E menunjukkan aktiviti antioksidan yang terkuat dengan nilai kepekatan untuk merencat 50% radikal pada 46.9 μg/mL, manakala ekstrak mentah etil asetat daripada kulit batang *Artocarpus maingayi* menunjukkan nilai kepekatan untuk merenct 50% radikal pada 60.1 μg/mL.

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LIST OF SYMBOLS/ ABBREVIATIONS/ TERMS

$AlCl_3$	Aluminium trichloride
AR	Analytical Grade
br	Broad
^{13}C	Carbon-13
CC	Column Chromatography
cm^{-1}	Per centimeter
cm	Centimeter
□C	Degree celcius
$CDCl_3$	Deuterated Chloroform
$CHCl_3$	Chloroform
CD3COCD3	Deuterated Acetone
CH_2Cl_2	Dichloromethane
COSY	Correlation Spectroscopy
d	Doublet
dd	Doublet of Doublet
DEPT	Distortionless Enhancement of Polarisation Transfer
DMSO	Dimethyl sulphoxide
DPPH	Diphenylpicrylhydrazyl
Et_2O	Diethyl Ether
EtOAc	Ethyl Acetate
EIMS	Electron Impact Mass Spectrometry
FTIR	Fourier Transform Infrared Red
GC	Gas Chromatography
GC-MS	Gas Chromatography-Mass Spectrometry
^1H	Proton
H_3BO_3	Boric Acid
HMBC	Heteronuclear Multiple Bond Correlation

HMQC	Heteronuclear Multiple Quantum Coherence
HRMS	High Resolution Mass Spectrometry
HCl	Hydrochloric Acid
IC	Inhibition Concentration
IR	Infrared
J	Coupling Constant
lit.	Literature
m	Multiplet
M	Molar
Mg	Milligram
MBC	Minimum bactericidal concentration
MIC	Minimum inhibition concentration
MeOH	Methanol
MHz	Megahertz
m.p	Melting point
m/z	Mass-to-charge ratio
NaOAc	Sodium Acetate
NaOMe	Sodium methoxide
Nm	Nanometer
NMR	Nuclear Magnetic Resonance
pet. Ether	Petroleum ether
ppm	Parts per million
R_f	Retention factor
s	Singlet
SC_{50}	Scavenging concentration to obtain 50% of the maximum scavenging capacity
t	Triplet
TLC	Thin Layer Chromatography
VLC	Vacuum Liquid Chromatography
UV	Ultraviolet
δ	Chemical Shift
μM	Micromolar
γ	Gamma
λ	Lambda

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CHAPTER 1

INTRODUCTION

1.1 General Introduction

Malaysia is included among the richest country with natural resources. It is abundant withvarious types of plants which are claimed to have medicinal properties including for beauty. About 125 000 types of plants were reported to have medicinal value or nutrition. In the past, people depended greatly on local flora and fauna for their survival. They used plants as food sources and medical purposes. All experience and knowledge passed down through mouth-to-mouth and in inherit hereditary. Nowdays, when world increasingly modern, human find new discovery on the plants. Many of the medicines were stimulated and researchers are racing to find solution for treating diseases of human being. Therefore, many researchs have been done on many types of rare plants in purpose to investigate the biologically active composition of the plants.

Many methods have been devised whereby the activity of a compound or extract from the plant can be tested scientifically. For the time being, natural product researchers from all over the world are struggling to find chemical compounds or active substances produced by plants or living organism where usually have pharmacological or biological activities for pharmaceutical usage. A natural product can be considered as such even if it can be prepared by total synthesis. Furthermore,

many plants distributed in Malaysia have many purposes either in pharmacological or in daily life. This included Moraceae plants which are widely distributed in Malaysia such as *Artocarpus integer* known as cempedak, and *Artocarpus communis* known as sukun.

1.2 Moraceace Family

Moraceace is one of the family plants that can be widely found in Malaysia. This family is flowering plants generally known as the mulberry family. The name Moraceace originated from the genus Morus. This family consists of eight recognizable genera which are *Antiaris, Artocarpus, Ficus, Hullettia, Morus, Parartocarpus, Prainea, and Streblus*. It comprises about 53 genera and 1400 species of plants which are mostly widespread in tropical and subtropical regions, but less common in temperate climates. There are 9 genera and 137 species of Moraceae family found in Malaysia's lowlands area to mountain forests [1].

Several members of this family constitute valuable timbers for commercial purposes such as *Artocarpus* and *Ficus*. *Artocarpus* is also known for its edible fruits such as *Artocarpus communis* (breadfruit or sukun), *A. heterophyllus* (jack-fruit or nangka), and *A. integer* (cempedak). A few of *Ficus* species is also known to give edible fruits and is used for birth control, as well as for women after giving birth and the leaves are consumed as tea [2].

1.3 Genus *Artocarpus*

The name '*Artocarpus*' is derived from the Greek word 'artos' and 'karpos' which means bread and fruit, respectively. Genus *Artocarpus* is classified into two subgenera which are *Artocarpus* and *Pseudojaca* by its morphological characters [3]. This genus comprises approximately 60 trees originated from South-East Asia, Western Pacific Islands, and widely distributed in Sri Lanka, India, Pakistan, Burma,

Thailand, Indo-China and Malaysia. Three species i.e. *Artocarpus communis, A. heterophyllus*, and *A. integer* are widely cultivated in the tropic. About 20 *Artocarpus* species are found in Malaysia including the cultivated widely species [1]. Several *Artocarpus* species distributed in Malaysia are listed in **Table 1.1**.

Table 1.1 : Several Malaysian *Artocarpus* Species **[4]**

Species	Distribution
A. bracteata (Ipoh)	Only in the North Malacca towards Seremban and in SingaporeIsland
A. champeden (Chempedak)	China, Malaysia, Sumatera, Coasts of New Guinea
A. communis (Sukun)	Cultivated throughout Malaysia
A. denisoniana (Nangka pipit)	North Selangor
A. elastica (Terap)	Cultivated throughout Malaysia
A. gomeziana (Tampang)	Tenasserim, Andamas to Borneo, Peninsular Malaysia
A. integra (Nangka)	Peninsular Malaysia, India, Sumatera
A. maingayi (Pudu)	Sumatera, Peninsular Malaysia, and Borneo
A. lanceifolius (Keledang)	Peninsular Malaysia and Singapore
A. lakoocha (Tampang)	Himalayas, Peninsular Malaysia
A. lowii (Miku)	Southern Thailand, Peninsular Malaysia, Borneo
A. rigida (Temponek)	India, south-eastwards to western Malaysia
A. scortechinii (Teraphitam)	Thailand, Peninsular Malaysia and Singapore
A. anisophylla (Tukul)	Peninsular Malaysia, Borneo, and Southern Philippine, Singapore

In the most recent revision of *Artocarpus* species, *Artocarpus communis* contains the following three species of breadfruit: *Artocarpus altilis, A. mariannensis* and *A. camansi* [5]. The plants of *Artocarpus* have been known to be used as traditional folk medicine in Southeast Asia for the treatment of inflammation, malarial fever, and also in treating ulcers, and diarrhea. While other members of the genus *Artocarpus* yield fairly good timber [5, 6]. Several isoprenylated flavonoids isolated from *Artocarpus* species indicated appealing biological activities such as anti-fungal [6], antinephritis [7], antimycobacterial [8], and anti-inflammatory [9].

1.4 Research Objectives

Artocarpus species were reported to contain hundreds of phenolic chemical constituents with a various biological activities such as antioxidant, anti-inflammatory, antibacterial, and cytotoxicity. However, most studies on the *Artocarpus* species were done by researchers from Indonesia and only a few literatures reported species from Malaysia which are *A.lowii* King [10], *A. Teysmanii* Miq. [11], and *A. scortechinii* King [12]. Since Malaysian *Artocarpus* species have not yet been intensively studied, this research will focus in identification of phytochemicals from *Artocarpus lanceifolius* and *Artocarpus maingayi*.

The objectives of this study are to extract the chemical constituents of *Artocarpus lanceifolius* and *A. maingayi* by using cold extraction with various organic solvents to obtain the crude extracts. All crude extracts will be fractionated by vacuum liquid chromatography (VLC). Fractions obtained from VLC will be purified by using various chromatographic techniques either on silica gel or Sephadex LH-20. The structures of the isolated compounds will be characterized by using spectroscopic techniques such as 1D and 2D NMR, FTIR, UV and MS. Finally, evaluation of the biological activities including antioxidant, and antibacterial of the crude extracts and pure compounds will be carried out.

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