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PHYTOCHEMICAL ANALYSIS OF AGLAIA MACROPHYLLA

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PHYTOCHEMICAL ANALYSIS OF *AGLAIA MACROPHYLLA*

By

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Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfillment of the requirement for the degree of Master of Science

PHYTOCHEMICAL ANALYSIS OF *AGLAIA MACROPHYLLA*

By

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October 2013

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The Meliaceae family, comprising of about 1400 species, is an important source of limonoids and tetranortriterpenoids. *Aglaia* is one of the genus within the family which has been the focus of phytochemical investigations due to its interesting biological activities. Certain species of *Aglaia* have traditionally been used for their medicinal and healing properties, such as for the treatment of fever, diarrhoea, inflammation and wounds. Although there has been many previous investigations on the genus, thus far, the species *A. macrophylla* has not been put through any phytochemical investigation. This species is a common species in Peninsular Malaysia. This work describes the phytochemical investigation on the methanolic bark extract of *Aglaia macrophylla*, leading to the isolation and identification of three new apotirucallane triterpenoids in addition to a known seco-limonoid. All compounds were identified by a combination of

spectroscopic methods including UV, IR, 1D and 2D NMR and ESI-MS as well as comparison with literature data.

The air-ground barks of *Aglaia macrophylla* were cold extracted by macerating in MeOH for several hours and repetitive cycles. The concentrated methanolic extract was partitioned into hexane, ethyl acetate and aqueous fractions. The hexane and ethyl acetate fractions were subjected to various chromatographic procedures which included vacuum liquid chromatography (VLC), column chromatography (CC) and finally, repetitive semi-preparative High Performance Liquid Chromatography (HPLC). The bark extract yielded four triterpenoids, one of which is a known seco-protolimonoid with a hemiacetal C-17 side chain, identified as methyl-1,7-diacetoxy-23,24,25-trihydroxy-20,21,24-epoxy-3,4-seco-apotirucall-4(28),14(15)-diene-3-oate **(56)**. The compound is a constituent of another Meliaceae species, *Trichilia elegans*. The other three compounds (**57**, **58** and **59**) are new, all possessing the same 3-oxoapotirucallane skeleton and carrying highly oxygenated C-17 side chains. The compounds were identified as 3,5,6-trihydroxy-6-methyl-2-(4,4,8,10,13-pentamethyl-3-oxo-1*H*-cyclopenta[*a*]phenanthren-17-yl) heptanoic acid **(57)**, 4,4,8,10,13-pentamethyl-17-(23,24,25-trihydroxy-20,21,24-epoxy)-2*H*-cyclopenta[*a*]phenanthren-3-one **(58)** and 4,4,8,10,13-pentamethyl-17-(3,5,6-trihydroxy-6-methylheptan-2-yl)-2*H*-cyclopenta[*a*]phenanthren-3-one **(59)**. Compound **58** was obtained from the hexane soluble fraction of the methanolic extract. The side chain was similar to the known **56** except for the loss of the hydroxyl group on C-24. Meanwhile, compounds **57** and **59** were isolated from the ethyl acetate soluble fraction. Compound **59** appears to be the C-21 oxidation product of **57**.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Master Sains

ANALISIS FITOKIMIA *AGLAIA MACROPHYLLA*

Oleh

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Oktober 2013

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Famili Meliaceae terdiri daripada 1400 spesis yang merupakan sumber penting untuk limonoid dan tetranortripenoid. *Aglaia* merupakan salah satu daripada genus dalam famili ini yang menjadi fokus kajian fitokimia bersesuaian dengan aktiviti biologinya yang menarik. Sesetengah spesis *Aglaia* telah digunakan secara tradisional untuk perubatan dan sifat penyembuhan seperti untuk merawati demam, cirit-birit, jangkitan dan luka. Selain itu, terdapat banyak kajian terdahulu berkenaan genus ini, setakat ini, spesis *A.macrophylla* belum melalui sebarang kajian fitokimia. Spesis ini merupakan spesis yang terdapat di Semenanjung Malaysia. Kajian ini menerangkan penyiasatan fitokimia terhadap ekstrak metanol bagi kulit kayu *Aglaia macrophylla*, membawa kepada pemencilan dan penemuan tiga sebatian baru apotirucallane triterpenoid sebagai tambahan kepada seco-limonoid. Semua sebatian telah dikenalpasti melalui gabungan

kaedah spektroskopi termasuk UV, IR, 1D dan 2D NMR dan ESIMS sebagai perbandingan dengan data analisis.

Kulit kayu *Aglaia macrophylla* diekstrakkan dengan rendaman di dalam MeOH untuk beberapa jam dan kitaran berulang-ulang. Ekstrak metanol pekat telah dipisahkan kepada pecahan heksana, etil asetat dan akueus. Pecahan heksana dan etil asetat tertakluk kepada pelbagai prosedur kromatografi termasuk vakum kromatografi cecair (VLC), kromatografi turus (CC) dan akhirnya, berulang-ulang semi-preparatif Kromatografi Cecair Prestasi Tinggi (HPLC). Ekstrak kulit kayu menghasilkan empat sebatian triterpenoid, salah satunya yang dikenali sebagai seko-protolimonoid dengan hemiasetal C-17 rantaian sampingan, yang dikenal pasti sebagai metil-1,7-diasetoksi-23,24,25-trihidroksi-20,21,24-epoksi-3,4-seko-apotirukal-4(28),14(15)-diene-3-oat (56). Sebatian ini adalah konstituen daripada spesies Meliaceae yang lain, *Trichilia elegans*. Tiga sebatian lain (57, 58 dan 59) adalah sebatian baru, semua memiliki rangka 3-oxoapotirucallane yang sama dan rantaian sampingan C-17 yang mempunyai kandungan oksigen yang tinggi. Sebatian telah dikenal pasti sebagai 3,5,6-trihidroksi-6-metil-2-(4,4,8,10,13-pentametil-oxo-1H-siklopenta [a] phenanthren-17-il) asid heptanoik (**57**), 4,4,8,10,13-pentametil-17-(23,24,25-trihidroksi-20,21,24-epoksi)-2H-siklopenta [a] phenanthren-3-one (**58**) dan 4,4,8,10,13-pentametil-17 (3,5,6-trihidroksi-6-metilheptan-2-il)-2H-siklopenta [a] penanthren-3-one (**59**). Sebatian 58 telah diperolehi daripada pecahan heksana yang larut dalam ekstrak metanol. Rantaian sampingan adalah serupa kepada sebatian 56 kecuali bagi kehilangan kumpulan hidroksi pada C-24. Sementara itu, sebatian 57 dan 59 telah diasingkan daripada pecahan etil asetat. Sebatian 59 muncul sebagai hasil pengoksidan C-21 bagi sebatian 57.

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This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfillment of the requirement for the degree of Master of Science. The members of Supervisory Committee were as follow:

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LIST OF ABBREVIATIONS

δ	Chemical shift in ppm
^{0}C	Degree in Celcius
bp	Boiling point
br	Broad
^{13}C	Carbon-13
COSY	Correlation Spectroscopy
d	Doublet
dd	Doublet of doublets
ddd	Doublet of doublets of doublets
dt	Doublet of triplets
eV	Electron volt
FT-IR	Fourier Transform Infra-Red
^{1}H	Proton
HMBC	Heteronuclear Multiple Bond Correlation
HSQC	Heteronuclear Single- Quantum Coherence
EIMS	Electron Impact Mass Spectrum
Hz	Hertz
IR	Infrared
J	Coupling constant in Hz

Lit.	Literature
m	multiplet
m/z	Mass per charge
MHz	Megahertz
m.p.	Melting point
MS	Mass spectrum
nm	Nanometer
NMR	Nuclear Magnetic Resonance
s	Singlet
t	Triplet
TLC	Thin Layer Chromatography
UV	Ultraviolet
UV/VIS	Ultraviolet/visible
VLC	Vacuum Liquid Chromatography

CHAPTER 1

INTRODUCTION

The use of natural products for therapeutic purposes is as ancient as human civilization and for a long time, mineral, plant and animal products were the main sources of drug. Even today, plants are the most important source of drug for the majority of the world's populations (Newman *et al*., 2003). Plants have been used for thousands of years to treat injuries and diseases. Despite the tremendous advances made by modern medical practices their contribution are still important until today (Soepadmo, 1992). The World Health Organization (WHO) estimated that, as much as 80% of the world population relies on the use of various forms of traditional or herbal medicine for its primary healthcare needs (Cragg *et al*., 1999; Narins, 2000).

An impressive number of modern drugs have been derived from natural sources based on their uses in traditional medicine. Thus, the best way to find new applications of plant derived drugs would seem to be the combination of local knowledge and the modern research techniques available today. General procedures of phytochemical analysis are shown in Figure 1.1.

Many researchers agree that isolation, purification and structural characterization of compounds are essential for finding new leads for drug discovery. The main objectives in the identifying compounds from the natural sources include :

1. the isolated compounds can be used as therapeutic agents.

2. the isolated compounds can be used as starting materials for the synthesis of useful drugs. As an example, adrenal cortex hormone is normally synthesized from steroidal sapogenin, which is isolated from plants.
3. the isolated compounds can become a model for a pharmacologically active molecular base for drugs synthesis. This is because some bioactive compounds may not be used as drug due to its side effects or limited bioavailability. Thus, structure modification is required to reduce toxicity or improve bioactivity. Furthermore, without information from these compounds, their drug activity and chemical characteristic will be impossible to establish. (Ahmad and Raji, 1993)

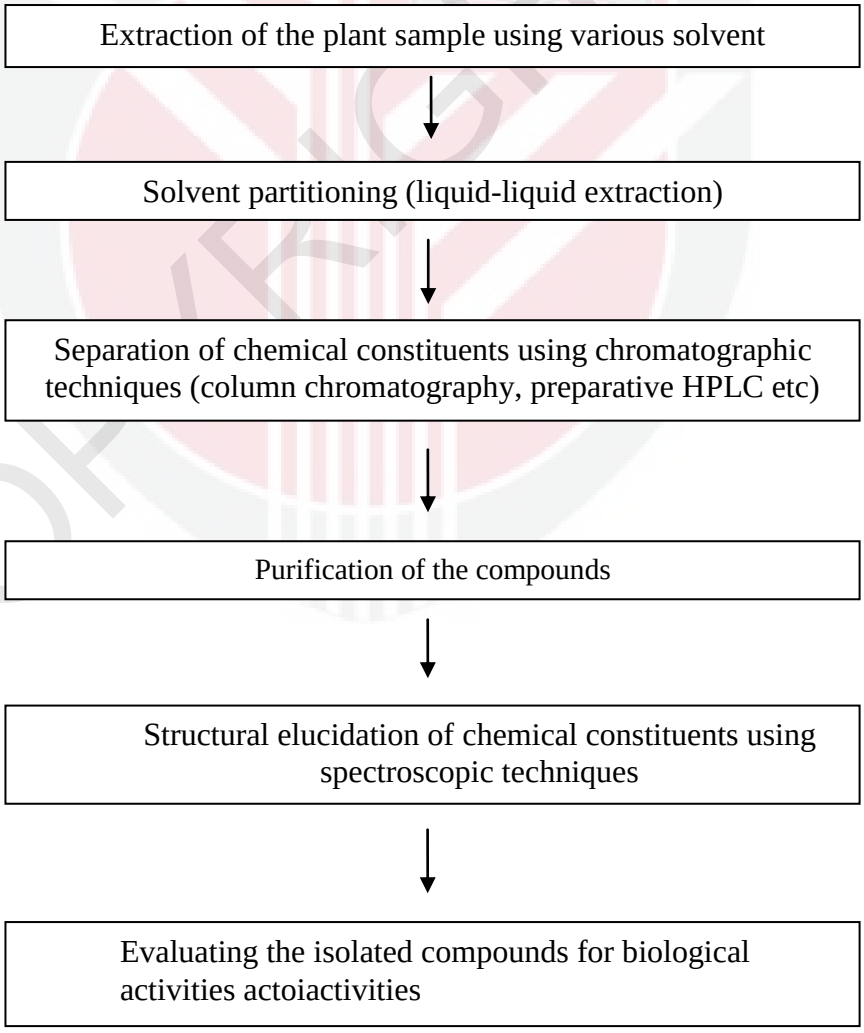

Figure 1.1 : General procedure for phytochemical analysis

Malaysia is considered to be one of the world's main hot spots for plant biodiversity because of its tropical rainforest. The tropical rainforest is well known to harbor a rich diversity not only at the level of the community but also at the family and genus levels. It is estimated that about 10,000 species are present in Peninsular Malaysia with at least 1,158 of them reported to have medicinal value. Apart from treating common illness such as coughs, colds, and headaches, many species are used for major diseases such as cancer and diabetes, as well as dangerous infectious diseases like cholera and malaria (Soepadmo, 1992).

Phytochemical screening of plants from the Meliaceae family indicated the presence of a diverse array of compound classes such as triterpenoids, alkaloids and saponins. From the many phytochemical reports on Meliaceae species, aromatic compounds with a cyclopenta(b)benzofuran skeleton represent typical chemical characteristic of the genus *Aglaia* (Nugroho *et al*., 1997a and 1997b). Based on the dehiscence of the fruit and the flower characters, a taxonomic monograph of the genus *Aglaia* recognizes two sections within this family, the section *Aglaia* (88 species) and the section *Amoora* (16 species) (Pannell *et al*., 1992). Some species are used in traditional medicine for the treatment of different diseases, including cancer, fever, heart problems, cough and inflammation. So far only representatives of the section *Aglaia* have been investigated phytochemically, wherein, various type of triterpenes (e.g., limonoids, cycloartanes, and tirucallanes) and cyclopenta(b)benzofurans have been largely isolated (Mulholland *et al*. 1993, Inada *et al*., 1997, Benosman *et al*., 1995).

Aglaia species form an important element of the moist tropical forest in the Indo-Malaysian region (Pannell *et al*., 1992). Several species, such as *A. odorata*, are traditionally used in folk medicine in south-east Asian countries (Kokpol *et al.*, 1994). Uses include, for example, as a heart stimulant and for the treatment of coughs. More recently, extracts from *Aglaia* species were shown to exhibit significant insecticidal activity towards several pest species (Champagne *et al*., 1989), suggesting that these plants may also be potential sources of natural insecticides. Aromatic compounds with a cyclopentatetrahydrobenzofuran skeleton, such as rocaglamide were subsequently shown to be responsible for the pronounced insecticidal activity of extracts derived from *A. odorata* (Janprasert *et al*., 1993).

Many previous phytochemical investigations on the genus *Aglaia* have been reported such as reports on *A. argentea,, A. duppereana, A. grandis, A. leucophylla, A. odorata, A. silvestris, A. oligophylla* and *A. edulis*.

Thus far, the species *A. macrophylla* has not been put through any phytochemical investigation. Therefore, the aim of this study is to identify the phytochemicals from *A. macrophylla*. Results obtained from this research would contribute to the scientific information on *Aglaia* species.

The objectives of this study are:

- to isolate chemical constituents from the extracts of *A. macrophylla* using various chromatographic methods.
- to elucidate the structures of the pure compounds isolated using spectroscopic techniques.

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