

EXTRACTION AND ISOLATION OF ALKALOIDS FROM THE LEAVES OF
Alseodaphne corneri (LAURACEAE)

JENNIE KHOO HUI CHEN

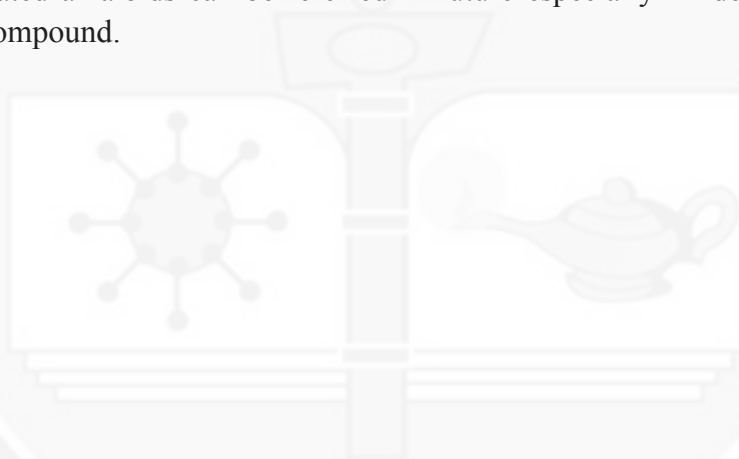
THESIS SUBMITTED IN FULFILLMENT OF THE REQUIREMENT FOR THE
DEGREE OF MASTER OF SCIENCE
(MASTER BY RESEARCH)

FACULTY OF SCIENCE AND MATHEMATICS
UNIVERSITI PENDIDIKAN SULTAN IDRIS

2015

ABSTRACT

This phytochemical study is aimed to extract, isolate and identify alkaloids from *Alseodaphne corneri* leaves. The crude alkaloid was extracted by cold percolation followed by acid-base extraction until Mayer test showed negative result. Then, it was separated by conventional chromatographic methods using column chromatography and preparative thin layer chromatography. The structural elucidation of isolated alkaloids was then carried out by spectroscopic techniques; UV, IR, NMR and HRESIMS. The structures of the compounds were also determined by comparison with previous study. Isolation of alkaloids yielded one new benzyloquinoline; (6,7-dimethoxyisoquinolinyl)-(2',5'-dihydroxy-4'-methoxyphenyl)-methanone **68**, one bisbenzyloquinoline; obamegine **49**, one oxoaporphines; atheroline **71**, and five aporphine; isocorydine **48**, *N*-methyllaurotetanine **51**, laurotetanine **53**, liriioferine **69** and norliriioferine **70**. The benzyloquinoline type alkaloid, liriioferine **69** and atheroline **71** were first reported in *Alseodaphne* genus while norliriioferine **70** was first isolated from *Alseodaphne corneri* species. These findings are very important as the elucidated alkaloids can be referred in future especially in identification of new alkaloid compound.



**PENGEKSTRAKAN DAN PEMENCILAN ALKALOID DARIPADA DAUN
Alseodaphne corneri (LAURACEAE)**

ABSTRAK

Kajian fitokimia ini bertujuan mengekstrak, memencil dan mengenal pasti alkaloid daripada daun *Alseodaphne corneri*. Alkaloid mentah diekstrak dengan menggunakan perkolasi sejuk diikuti pengekstrakan asid-bes sehingga ujian Mayer menunjukkan keputusan negatif. Seterusnya, alkaloid mentah dipencilkan melalui kaedah kromatografi konvensional dengan menggunakan kromatografi kolom dan kromatografi lapis tipis preparatif. Pengenalpastian struktur alkaloid yang dipencil dilakukan dengan teknik-teknik spektroskopi seperti UV, IR, NMR dan HRESIMS. Struktur sebatian yang dikenalpasti turut dibandingkan dengan kajian-kajian lepas. Pengasingan alkaloid telah menghasilkan satu benzilisokuinolina; (6,7-dimetoksiisokuinolil)-(2',5'-dihidroksi-4'-metoksifenil)-metanon **68**, satu bisbenzilisokuinolina; obamegina **49**, satu oxoaporphina; aterolina **71**, serta lima aporphina; isocoridina **48**, *N*-metillaurotetanina **51**, laurotetanina **53**, liriioferina **69** dan norliriioferina **70**. Alkaloid jenis benzilisokuinolina, liriioferina **69** dan aterolina **71** adalah kali pertama dilaporkan dalam genus *Alseodaphne* manakala norliriioferina **70** adalah kali pertama diekstrak daripada spesies *Alseodaphne corneri*. Penemuan ini amat penting kerana data alkaloid yang dikenal pasti boleh dijadikan rujukan untuk masa depan terutamanya dalam pengenalpastian sebatian alkaloid baru.

UNIVERSITI PENDIDIKAN SULTAN IDRIS UNIVERSITI PENDIDIKAN SULTAN IDRIS UNIVERSITI PENDIDIKAN SULTAN IDRIS UNIVERSITI PENDIDIKAN SULTAN IDRIS

CONTENTS

	Page
ACKNOWLEDGEMENT	iii
ABSTRACT	iv
ABSTRAK	v
CONTENTS	vi
LIST OF TABLES	ix
LIST OF FIGURES	x
LIST OF SYMBOLS AND ABBREVIATIONS	xiv
CHAPTER 1 INTRODUCTION	
1.1 Introduction	1
1.2 Problem Statement	3
1.3 Objectives	3
1.4 Lauraceae	3
1.5 The Genus: <i>Alseodaphne</i>	5
1.5.1 <i>Alseodaphne corneri</i>	7
CHAPTER 2 LITERATURE REVIEW	
2.1 Introduction	9
2.2 Nitrogen Containing Compounds	12
2.3 Classification of Alkaloids	13
2.3.1 Isoquinoline Alkaloids	15
2.3.2 Benzylisoquinoline	17

2.3.3	Bisbenzylisoquinoline alkaloids	17
2.3.4	Aporphinoid alkaloids	21
2.4	<i>Alseodaphne corneri</i>	23

CHAPTER 3 EXPERIMENTAL

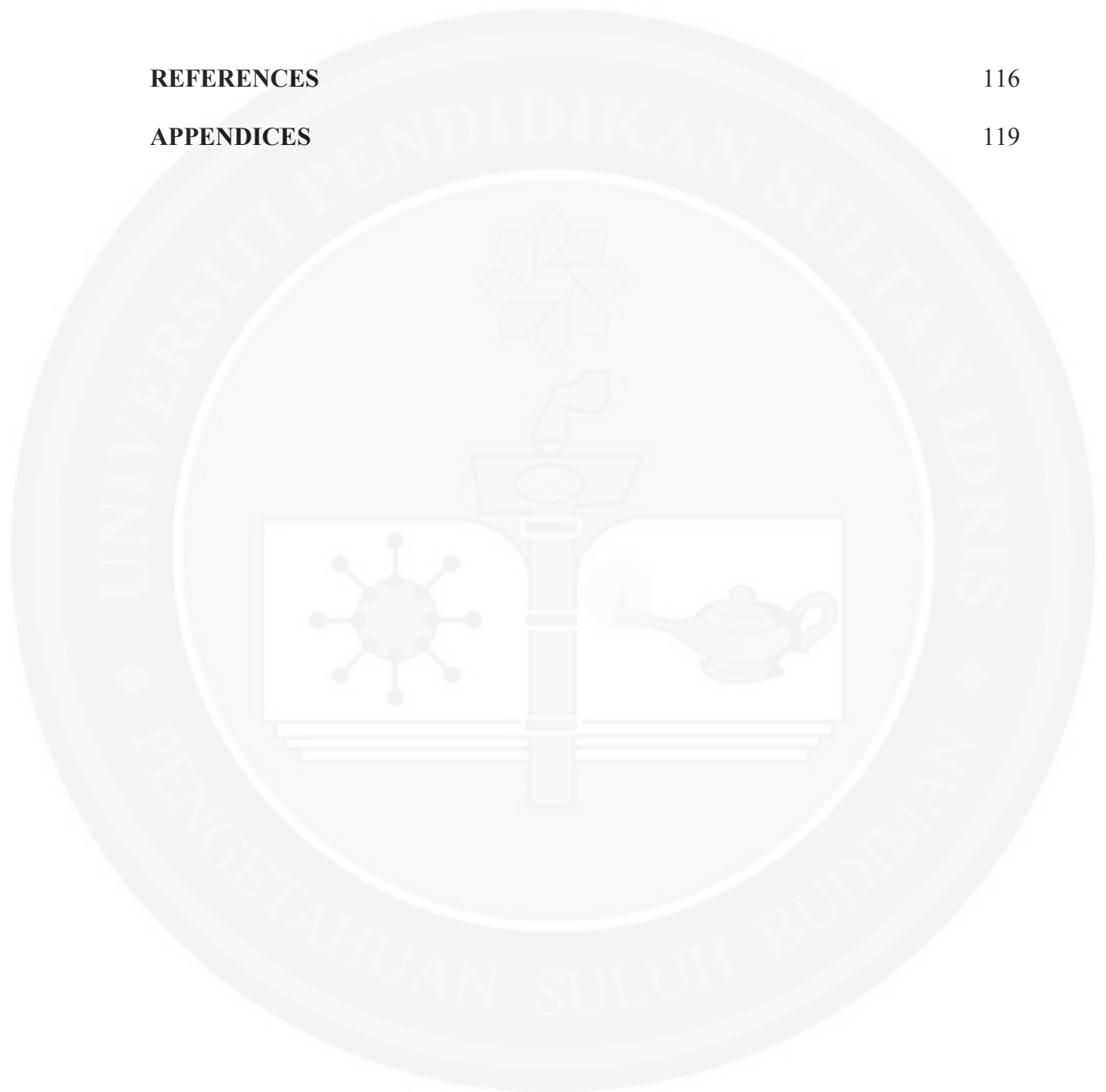
3.1	Introduction	29
3.2	Chemical Reagents	30
3.3	Plant Materials	32
3.4	Extraction of Plants Material	32
3.5	Separation and Purification of Alkaloids	33
3.6	Physical and Spectral Data of the Isolated Compounds	35

CHAPTER 4 RESULTS AND DISCUSSION

4.1	Introduction	41
4.2	Alkaloids from the Leaves of <i>Alseodaphne corneri</i>	44
4.2.1	Isocorydine 48	44
4.2.2	Obamegine 49	53
4.2.3	<i>N</i> -Methylaurotetanine 51	63
4.2.4	Laurotetanine 53	72
4.2.5	(6,7-dimethoxyisoquinolinyl)-(2',5'-dihydroxy-4'-methoxyphenyl)-methanone 68	79
4.2.6	Lirioferine 69	88
4.2.7	Norlirioferine 70	97

UNIVERSITI PENDIDIKAN SULTAN IDRIS	UNIVERSITI PENDIDIKAN SULTAN IDRIS	UNIVERSITI PENDIDIKAN SULTAN IDRIS	UNIVERSITI PENDIDIKAN SULTAN IDRIS
UNIVERSITI PENDIDIKAN SULTAN IDRIS	UNIVERSITI PENDIDIKAN SULTAN IDRIS	UNIVERSITI PENDIDIKAN SULTAN IDRIS	UNIVERSITI PENDIDIKAN SULTAN IDRIS
UNIVERSITI PENDIDIKAN SULTAN IDRIS	UNIVERSITI PENDIDIKAN SULTAN IDRIS	UNIVERSITI PENDIDIKAN SULTAN IDRIS	UNIVERSITI PENDIDIKAN SULTAN IDRIS
UNIVERSITI PENDIDIKAN SULTAN IDRIS	UNIVERSITI PENDIDIKAN SULTAN IDRIS	UNIVERSITI PENDIDIKAN SULTAN IDRIS	UNIVERSITI PENDIDIKAN SULTAN IDRIS

4.2.8 Atheroline	71	106
CHAPTER 5 CONCLUSION AND RECOMMENDATION		114
REFERENCES		116
APPENDICES		119



LIST OF TABLES

TABLE	PAGE
2.1 Alkaloids from <i>A. corneri</i>	24
3.1 Mayer's Test on Alkaloid	31
4.1 ^1H NMR and ^{13}C NMR spectral data of 48 and isocorydine (Nafiah, 2009)	52
4.2 ^{13}C NMR spectral data of 49 and obamegine (Nafiah, 2009)	61
4.3 1D (^1H and ^{13}C) and 2D (HMBC, HMQC and COSY) NMR spectral data of 49	62
4.4 1D (^1H and ^{13}C) and 2D (HMBC and HMQC) NMR spectral data of 51	71
4.5 ^1H NMR and ^{13}C NMR spectral data of 53 and ^{13}C NMR data of laurotetanine (Zahari, 2010)	78
4.6 1D (^1H and ^{13}C) and 2D (HMBC and HMQC) NMR spectral data of 68	87
4.7 ^1H NMR and ^{13}C NMR spectral data of 69 and lirioferine (Saidi et al., 2009)	96
4.8 1D (^1H and ^{13}C) and 2D (HMBC and HMQC) NMR spectral data of 70	105
4.9 ^1H NMR and ^{13}C NMR spectral data of 71 and ^1H NMR data of atheroline (Saidi, 2011)	113

LIST OF FIGURES

FIGURE

1.1	<i>Alseodaphne corneri</i> Kosterm	8
1.2	The leaves and fruit of <i>Alseodaphne corneri</i> Kosterm	8
2.1	The numbering system of isoquinoline alkaloid	15
2.2	The biosynthesis of isoquinoline alkaloids	16
2.3	The numbering system of the benzyloisoquinoline alkaloid	17
2.4	The numbering system of the half dimer of bisbenzyloisoquinoline alkaloid	18
2.5	The numbering system of bisbenzyloisoquinoline alkaloid	19
2.6	The oxoaporphine alkaloid	22
2.7	The numbering system of aporphine alkaloid	22
3.1	Isolation of alkaloids from <i>A. corneri</i>	34
4.1	UV Spectrum of 48	46
4.2	IR Spectrum of 48	47
4.3	HRESIMS Spectrum of 48	47
4.4	¹ H NMR Spectrum of 48	48
4.5	¹³ C NMR Spectrum of 48	49
4.6	DEPT NMR Spectrum of 48	49
4.7	COSY NMR Spectrum of 48	50
4.8	HMQC NMR Spectrum of 48	50
4.9	HMBC NMR Spectrum of 48	51
4.10	¹ H- ¹³ C Correlations observed in HMBC NMR spectrum of 48	51
4.11	IR Spectrum of 49	55

UNIVERSITI PENDIDIKAN SULTAN IDRIS	UNIVERSITI PENDIDIKAN SULTAN IDRIS	UNIVERSITI PENDIDIKAN SULTAN IDRIS	UNIVERSITI PENDIDIKAN SULTAN IDRIS
N IDRIS	UNIVERSITI PENDIDIKAN SULTAN IDRIS	UNIVERSITI PENDIDIKAN SULTAN IDRIS	UNIVERSITI F
4.12	UV Spectrum of 49		55
4.13	HRESIMS Spectrum of 49		56
4.14	¹ H NMR Spectrum of 49		57
4.15	¹³ C NMR Spectrum of 49		58
4.16	DEPT NMR Spectrum of 49		58
4.17	COSY NMR Spectrum of 49		59
4.18	HMQC NMR Spectrum of 49		59
4.19	HMBC NMR Spectrum of 49		60
4.20	¹ H- ¹³ C Correlations observed in HMBC NMR spectrum of 49		60
4.21	IR Spectrum of 51		65
4.22	UV Spectrum of 51		65
4.23	HRESIMS Spectrum of 51		66
4.24	¹ H NMR Spectrum of 51		67
4.25	¹³ C NMR Spectrum of 51		68
4.26	DEPT NMR Spectrum of 51		68
4.27	COSY NMR Spectrum of 51		69
4.28	HMQC NMR Spectrum of 51		69
4.29	HMBC NMR Spectrum of 51		70
4.30	¹ H- ¹³ C Correlations observed in HMBC NMR spectrum of 51		70
4.31	IR Spectrum of 53		73
4.32	UV Spectrum of 53		74
4.33	HRESIMS Spectrum of 53		74
4.34	¹ H NMR Spectrum of 53		75
4.35	¹³ C NMR Spectrum of 53		76
4.36	DEPT NMR Spectrum of 53		76

UNIVERSITI PENDIDIKAN SULTAN IDRIS	UNIVERSITI PENDIDIKAN SULTAN IDRIS	UNIVERSITI PENDIDIKAN SULTAN IDRIS	UNIVERSITI PENDIDIKAN SULTAN IDRIS
N IDRIS	UNIVERSITI PENDIDIKAN SULTAN IDRIS	UNIVERSITI PENDIDIKAN SULTAN IDRIS	UNIVERSITI F
4.37	HMQC NMR Spectrum of 53		77
4.38	HMBC NMR Spectrum of 53		77
4.39	^1H - ^{13}C Correlations observed in HMBC NMR spectrum of 53		78
4.40	IR Spectrum of 68		81
4.41	UV Spectrum of 68		81
4.42	HRESIMS Spectrum of 68		82
4.43	^1H NMR Spectrum of 68		83
4.44	^{13}C NMR Spectrum of 68		84
4.45	DEPT NMR Spectrum of 68		84
4.46	COSY NMR Spectrum of 68		85
4.47	NOESY NMR Spectrum of 68		85
4.48	HMQC NMR Spectrum of 68		86
4.49	HMBC NMR Spectrum of 68		86
4.50	^1H - ^{13}C Correlations observed in HMBC NMR spectrum of 68		87
4.51	IR Spectrum of 69		90
4.52	UV Spectrum of 69		90
4.53	HRESIMS Spectrum of 69		91
4.54	^1H NMR Spectrum of 69		92
4.55	^{13}C NMR Spectrum of 69		93
4.56	DEPT NMR Spectrum of 69		93
4.57	COSY NMR Spectrum of 69		94
4.58	HMQC NMR Spectrum of 69		94
4.59	HMBC NMR Spectrum of 69		95
4.60	^1H - ^{13}C Correlations observed in HMBC NMR spectrum of 69		95
4.61	IR Spectrum of 70		99

UNIVERSITI PENDIDIKAN SULTAN IDRIS	UNIVERSITI PENDIDIKAN SULTAN IDRIS	UNIVERSITI PENDIDIKAN SULTAN IDRIS	UNIVERSITI PENDIDIKAN SULTAN IDRIS
N IDRIS	UNIVERSITI PENDIDIKAN SULTAN IDRIS	UNIVERSITI PENDIDIKAN SULTAN IDRIS	UNIVERSITI PENDIDIKAN SULTAN IDRIS
4.62	UV Spectrum of 70		99
4.63	HRESIMS Spectrum of 70		100
4.64	¹ H NMR Spectrum of 70		101
4.65	¹³ C NMR Spectrum of 70		102
4.66	DEPT NMR Spectrum of 70		102
4.67	COSY NMR Spectrum of 70		103
4.68	HMQC NMR Spectrum of 70		103
4.69	HMBC NMR Spectrum of 70		104
4.70	¹ H- ¹³ C Correlations observed in HMBC spectrum of 70		104
4.71	IR Spectrum of 71		108
4.72	UV Spectrum of 71		108
4.73	HRESIMS Spectrum of 71		109
4.74	¹ H NMR Spectrum of 71		110
4.75	¹³ C NMR Spectrum of 71		111
4.76	COSY NMR Spectrum of 71		111
4.77	HMQC NMR Spectrum of 71		112
4.78	HMBC NMR Spectrum of 71		112
4.79	¹ H- ¹³ C Correlations observed in HMBC NMR spectrum of 71		113

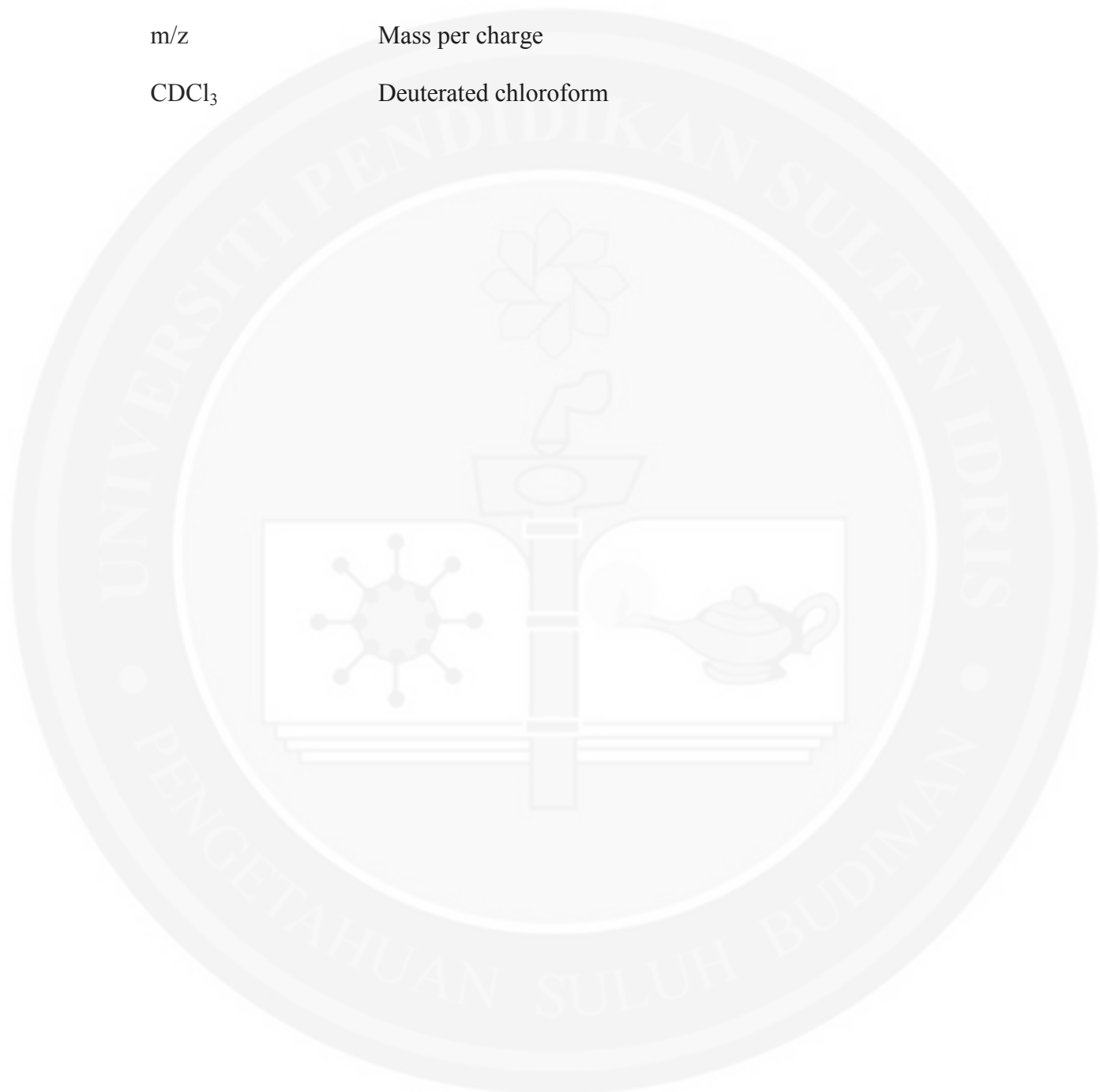
UNIVERSITI PENDIDIKAN SULTAN IDRIS UNIVERSITI PENDIDIKAN SULTAN IDRIS UNIVERSITI PENDIDIKAN SULTAN IDRIS UNIVERSITI PENDIDIKAN SULTAN IDRIS

LIST OF SYMBOLS AND ABBREVIATIONS

α	Alpha
β	Beta
λ	Maximum wave length
δ	Chemical shift
g	Gram
kg	Kilogram
M	Molar
mM	Milimolar
ml	Mililitre
m	Meter
MHz	Mega Hertz
Hz	Hertz
UV	Ultraviolet
IR	Infrared
ppm	Part per million
eV	Electron Volt
MeOH	Methanol
CHCl ₃	Chloroform
CH ₂ Cl ₂	Dichloromethane
CH ₃	Methyl group
OCH ₃	Methoxyl group
Me	Methyl group
OMe	Methoxyl group

OH	Hydroxyl group
NH ₃	Ammonia
pH	Power of Hydrogen
HCl	Hydrogen chloride
TLC	Thin Layer Chromatography
PTLC	Preparative Thin Layer Chromatography
CC	Column Chromatography
NMR	Nuclear Magnetic Resonance
cm ⁻¹	Per centimeter
<i>J</i>	Coupling constant
<i>d</i>	Doublet
<i>dd</i>	Doublet of doublet
<i>t</i>	Triplet
<i>dt</i>	Doublet of triplet
<i>s</i>	Singlet
<i>m</i>	Multiplet
°C	Degree Celsius
1D-NMR	One Dimension Nuclear Magnetic Resonance
2D-NMR	Two Dimension Nuclear Magnetic Resonance
¹ H	Proton NMR
¹³ C	13-Carbon NMR
COSY	¹ H- ¹ H Correlation Spectroscopy
DEPT	Distortionless Enhancement by Polarization Transfer
HMQC	Heteronuclear Multiple Quantum Correlation
HMBC	Heteronuclear Multiple Bond Correlation

NOESY	Nuclear Overhauser Effect Spectroscopy
LC-MS	Liquid Chromatography Mass Spectrometry
HRESIMS	High Resolution Electrospray Ionization Mass Spectrometry
m/z	Mass per charge
CDCl ₃	Deuterated chloroform



CHAPTER 1

INTRODUCTION

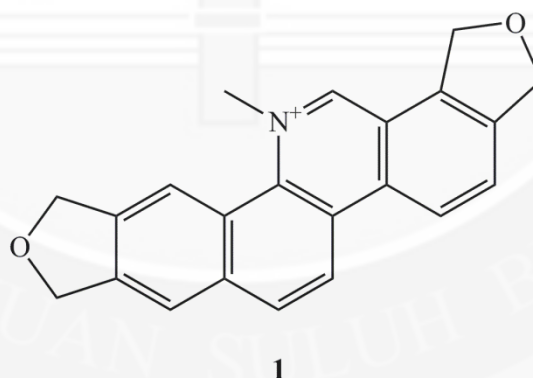
1.1 Introduction

Malaysia is located near the Equator confers on it a typically tropical climate which contributes to the tropical rainforests. This country is rich in flora and estimated to have 17,631 species of plants; including 61 gymnosperm, 337 of algae, 1,387 bryophyte, 1,600 species ferns and its families, 4,180 monocotyledons and 10,026 dicotyledons, thus, the 2001 Global Diversity Outlook recognized Malaysia as one of 12 mega diversity countries in the world (Department of Statistics, Malaysia, 2012).

Plants are usually used as traditional medicines or herbs for treatment, recovery and health maintenance of many diseases since ancient times. During Ming Dynasty, S.Z, Li had been compiled and written traditional Chinese medicine book titled 'Compendium of Materia Medica'. This compendium recorded the plants,

animals, minerals and other objects which believed to have medicinal properties (“Ben Cao Gang Mu (Compendium of Materia Medica),” 2011). In Malaysia, there are some common traditional medicinal plants used to cure many diseases such as diabetes treatment using *misai kucing* (*Orthosiphon stamineus*) (Ching, Zakaria, Paimin, & Jalalian, 2013). Besides traditional medicines, many plants have been proven the presence of biologically active compounds; for example, Sanguinarine **1** from Papaveracea family exhibit anticancer properties (Lu, Bao, Chen, Huang, & Wang, 2012).

The natural resources (especially from plants) provide rich source of new pharmaceuticals, agrochemicals, industrial raw material and other economically important products. Recently, "Back to Nature" becomes a trend for the public. Therefore, natural products are one of the most promising sources for discovery of future drugs in various therapeutic areas.



1.2 Problem Statement

The phytochemical studies on *Alseodaphne corneri* have been published since 2008. Twenty-two compounds, mainly isoquinoline type alkaloids were reported on this species and nine known compounds were isolated from the leaves of *A. corneri*. From the preliminary screening, the leaves of this species have high content of alkaloids. Therefore, it is a potential plant for extraction and isolation followed by structural elucidation of alkaloids especially the new compound as reference in future.

1.3 Objectives

The objectives of this study are as follows:

- i. To extract alkaloid from the leaves of *Alseodaphne corneri*.
- ii. To isolate alkaloids from the crude samples using chromatographic techniques.
- iii. To carry out structural elucidation of isolated alkaloids.

1.4 Lauraceae

Lauraceae, named from the famous laural cultivated from centuries in Europe, usually appear as tropical evergreen shrubs or trees except in temperate zones which is deciduous. In past, its foliage was used by the ancient Greeks to crown victors in athlete events (Dharmananda, 2004). Later on, it was used in the conferring of academic honors. Nowadays, Lauraceae becomes important sources of traditional

UNIVERSITI PENDIDIKAN SULTAN IDRIS UNIVERSITI PENDIDIKAN SULTAN IDRIS UNIVERSITI PENDIDIKAN SULTAN IDRIS UNIVERSITI PENDIDIKAN SULTAN IDRIS

medicines (e.g. *Lindera aggregata*), timber, spices (e.g. *Cinnamomum* trees), nutritious fruits (e.g. *Persea americana*) and perfumes (Xiwen et al., 2000).

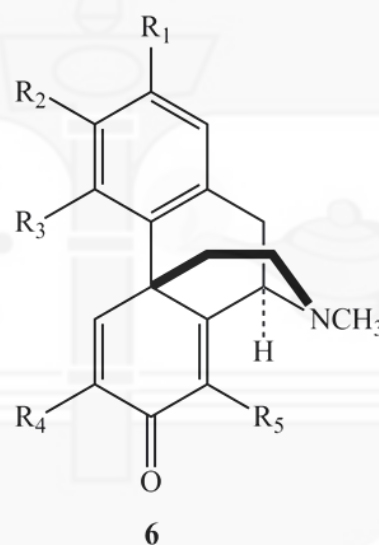
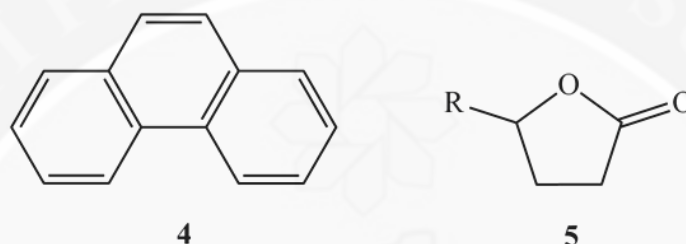
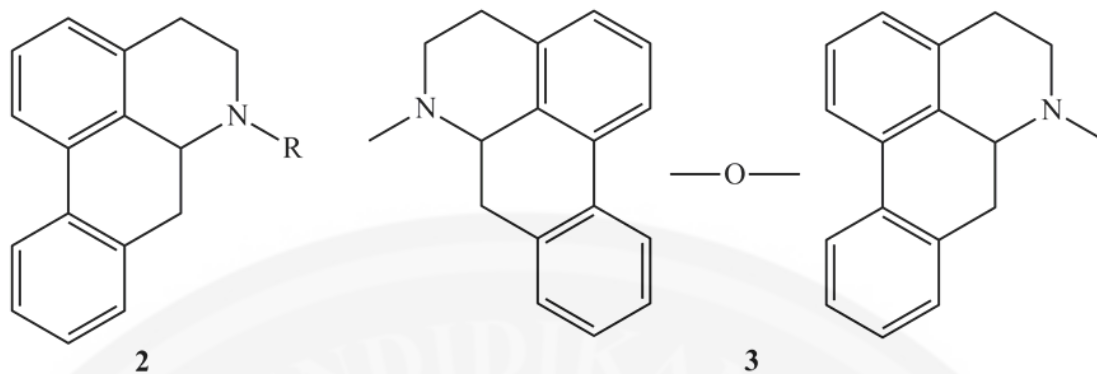
The laurel order of flowering plants contains 7 families, 91 genera and about 2900 species. They are found in tropical or warm temperate climates, abundant in regions with moist equable climates. The members of Laurales are trees, shrubs or woody vines and they are characterized by woodiness, aromatic parts and a single strand of conducting tissues continuing from the stem into the leaf. Among seven families, both Lauraceae and Monimiaceae constitute most of the genera in this order. Lauraceae consists of 67 genera distributed throughout tropical and subtropical regions, principally Southeast Asia and tropical America, particularly Brazil. In 1970, Keng (as cited in Perumal, Petol, Mat-Salleh, & Latiff, 1998) reported that Lauraceae belongs to ten most extensive genera in Malaysia.

Leaves of Lauraceae family usually alternate, occasionally opposite or subopposite or verticillate, simple, usually entire, rarely lobed. The flowers are perigynous and cup-like structure around the base of ovary or around ovary. In addition, they usually exist as axillary. Drupe or berry like fruit usually surrounded at base by enlarge and often persistent perianth tube seated on a large receptacle or pedicel (Xiwen et al., 2000).

1.5 The Genus: *Alseodaphne*

Alseodaphne is a member of family Lauraceae and distributed in tropical belt of India, Cambodia, China, Indonesia, Laos, Malaysia, Myanmar and Philipines. Most of these species are locally known as "Medang" or "Tejur" in Malaysia. There are 23 out of 56 species are found in Malaysia (Nafiah, 2009).

The plants are source of wood (contributes in house and boat building) and furniture such as plywood tea-chest. Many researchers have been explored this species. However, very less species have been reported their chemical composition. Recently, chemical constituents were reported from the isolation of some species such as *A. archboldina*, *A. andersonii*, *A. corneri*, *A. hainensis*, *A. pendulifolia*, *A. penduncularis*, *A. perenkensis* and *A. semicarpifolia*. This genus were reported rich to contain aporphines **2**, bisbenzylisoquinolines **3**, phenanthrenes **4**, lactones **5** and morphinandienones **6**; which could be of great biological importance. Although the fruits of *A. corneri* were known to be poisonous, there are still no report on biological study and medicinal value of this species (Thakur et al., 2012).



Alseodaphne is small to medium sized tree of wet evergreen tropical forests which distributed from Yunnan to West Malaysia. It normally 5-35 meters height (Nafiah et al., 2011). The leaves are broad and alternate which mostly clustered near apex of branchlets. Terminal buds are scaly whereas inflorescences are axillary, paniculate or racemose. Flowers are bisexual, trimerous and short perianth tube with six lobes which are sub-equal and absent in fruit. There are nine fertile stamens in

three whorls with filaments of first and second whorls are glandless. Anthers are four celled. The ovary is partly immersed into shallow perianth tube. The style is as long as ovary. The stigma is small and inconspicuous. The fruits are green when unripe and purplish black when mature with ovoid, oblong or sub-globose in shape (Nafiah, 2009; Thakur et al., 2012; Zahari, 2010).

1.5.1 *Alseodaphne corneri*

Alseodaphne corneri (Figure 1.1) is a small tree up to 6 m tall which is found in Malaysia, Singapore and Indonesia. Terminal bud covered with many 1 cm long glabrous scales. The twigs are stout and grey colour with prominent leaf scars. The leaves (Figure 1.2) are closely, spirally arranged at end of twigs, stalk is about 3-4 cm long and blade thickly leathery with obovate to elliptic shape and about 28-52 x 12-16 cm. The apex is pointed but the base is tapered and glaucous below. The midrib rose on the upper surface consists of about 22 pairs of secondary nerves which rise on both surfaces. Tertiary nerves reticulate, visible on both surfaces (Thakur et al., 2012).

The flowers of this species are glaucous up to 14 mm long. Perianth lobes equal, oblong with 5 mm long. The fruits (Figure 1.2) of this species are ellipsoid which up to 3 x 2 cm, seated on very thick, rough, warted and pedicel with persistent perianth lobes. *Alseodaphne corneri* is very rare and the plant specimens are from lowland in East Malaysia especially in east Johor (Nafiah, 2009; Zahari, 2010).



Figure 1.1. Alseodaphne corneri Kosterm.



Figure 1.2. The leaves and fruit of Alseodaphne corneri Kosterm.

CHAPTER 2

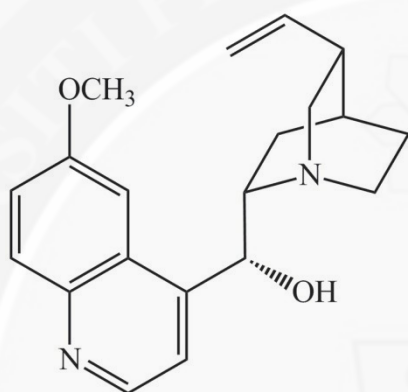
LITERATURE REVIEW

2.1 Introduction

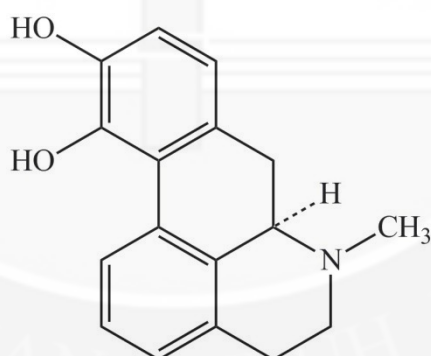
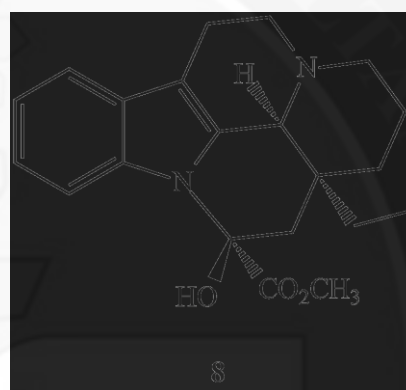
Since ancient times, plants are always consumed for health purposes. After the plants have been extracted and studied, scientists found compounds and related them to the medicinal treatment. These compounds are clinically useful drug such as antimalarian agents (e.g. quinine **7**), agents promoting blood circulation in the brain (e.g. vincamine **8**), in Parkinson's disease treatment (e.g. apomorphine **9**) and anticancer agents (e.g. taxol **10**) (Aniszewski, 2007; Bently, 1998). The drug discovery from natural product experienced an evolution in the last decade and now it is widely accepted due to its potential in many therapeutic areas (Genilloud & Vicente, 2012).

In 1804, morphine **11** had been isolated from opium poppy. It is the first alkaloid that isolated and crystallized from plant. Then, the medicinal properties of

morphine were studied and researcher found that morphine **11** is a powerful narcotic used to relief pain. Later on, many alkaloids were reported and their medicinal properties were identified such as quinine **7** from genus *Cinchona* is used to treat arrhythmias or irregular rhythms of the heartbeat, ephedrine **12** from *Ephedra* species act as blood-vessel constrictors and so on (“Alkaloid,” 2013; Nafiah, 2009).



7



9