PHYTOCHEMICAL, BIOLOGICAL, STABILITY AND PHARMACOKINETIC STUDIES ON THE EXTRACTS OF THREE VARIETIES OF *Ficus deltoidea* Jack LEAVES

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Dedicated to

My parents, brothers and sisters

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بِسْمِ ٱللهِ ٱلرَّحْمَـٰنِ ٱلرَّحِيمِ

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ACE	angiotensin converting enzyme
ALL	allopurinol
ATR	attenuated total reflectance
BHA	butylated hydroxyanisole
BHT	butylated hydroxytoluene
BSA	bovine serum albumin
COSY	Correlation spectroscopy
COX	cycloxygenase
DEPT	Distortionless Enhancement by Polarization Transfer
DMSO-d_6	deuterated dimethyl sulfoxide
DNA	deoxyribonucleic acid
DPPH	1,1-diphenyl-2-picrylhydrazyl
EIMS	electron ionization mass spectrometry
EMEA	European Agency for the Evaluation of Medicinal Products
FD	*Ficus deltoidea*
FDA	Food and Drug Administration
FDLNA	*Ficus deltoidea* var. *terengganuensis* 1
FDLNAM	methanol extracts of FDLNA
FDLNAW	water extracts of FDLNA
FDLNHT	*Ficus deltoidea* var. *deltoidea*
FDLNHTM	methanol extracts of FDLNHT
FDLNHTW	water extracts of FDLNHT
FDLSPLS	*Ficus deltoidea* var. *terengganuensis* 2
FDLSPLSM	methanol extracts of FDLSPLS
FDLSPLSW	water extracts of FDLSPLS
FDLTK	*Ficus deltoidea* var. *angustifolia*
FDLTKSM	methanol extracts of FDLTKS
FDLTKSW	water extracts of FDLTKS
GA	gallic acid
HHL	hippuryl-histidyl-leucine
HIFBS	heat inactivated fetal bovine serum
HYAase	Hyaluronidase
ICH	International Council of Harmonization
LOD	limit of detection
LOQ	limit of quantification
LOX	Lipoxygenase
NBT	nitroblue tetrazolium
NMR	nuclear magnetic resonance
NO	nitric oxide
NOSs	nitric oxide synthases
NP	natural products
OECD	Organization for Economic Co-operation and Development
o-H_3PO_4	ortho – phosphoric acid
PBS	phosphate buffer saline
PCA	principal component analysis
PDA	photo diode array
PTFE	Polytetrafluoroethylene
QTN	Quercetin
R.S.D	relative standard deviation
RH	relative humidity
RNS	reactive nitrogen species
ROS	reactive oxygen species
SD	standard deviation

SOD	superoxide anion
TPA	12-O-tetradecanoylphorbol-13 acetate
WHO	World Health Organization
XOD	xanthine oxidase

LIST OF PUBLICATIONS AND SEMINARS

Working Papers:

1. Zunoliza Abdullah, Zhari Ismail and Rasadah Mat Ali (2007) Total Flavonoids, Polyphenols, Tannins and Antioxidants properties of *Ficus deltoidea.* USM-UNAIR First Collaborative Conference, 13-14 June 2007, Penang. Biotechnology and Pharmaceuticals: enhancing the life. (Oral presentation)

2. Zunoliza Abdullah, Zhari Ismail and Rasadah Mat Ali (2006) Preliminary Results from a Study on Standardization of Malaysian Medicinal Plant, *Ficus deltoidea.* (2006) 3rd Life Sciences Postgraduate Seminar in conjunction with 1st USM Penang International Postgraduate Conference, Penang, 24-27 May 2006.

3. Zunoliza Abdullah, Zhari Ismail & Rasadah Mat Ali (2007).HPLC and HPTLC Profiling and free radical scavenging of Alcohol and Aqueous Extracts of *Ficus deltoidea* spp. Poster presented at *at International Symposium on Natural Products and Medicinal Chemistry (NPMC) 2007 in conjunction with* 12th Asian Chemical Congress (12ACC) 23-25 August 2007. *Putra World Trade Centre, Kuala Lumpur, Malaysia.*

4. Zunoliza Abdullah, Zhari Ismail, Rasadah Mat Ali, Dr. Amin Malik Abdul Majid, Hayder B. Sahib (2008) Direct UV spectrophotometric evaluation of ACE inhibitory activity and determination of antiangiogenesis activity of *Ficus deltoidea* leaves extracts. Poster presented at 4th Life Sciences Postgraduate Seminar in conjunction with 2nd USM Penang International Postgraduate Conference, 18th - 20th June 2008.

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2. Abdullah Zunoliza, Hussain Khalid**,** Ismail Zhari**,** Mat Ali Rasadah, Pisar Mazura, Jamaludin Fadzureena, Sahdan Rohana (2009) Evaluation of extracts of leaf of three *Ficus deltoidea* varieties for antioxidant activities and secondary metabolites. Pharmacognosy Magazine, 1, 216-223.

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KAJIAN FITOKIMIA, BIOLOGIKAL, KESTABILAN DAN FARMAKOKINETIK EKSTRAK-EKSTRAK TIGA VARIASI DAUN *Ficus deltoidea* Jack

ABSTRAK

Kajian ini telah dijalankan bagi memberikan maklumat terhadap pemiawaian esktrak daun *Ficus deltoidea* (*FD*). Tiga variasi pokok iaitu *FD* var. *terengganuensis*, *FD* var. *angustifolia* dan *FD* var. *deltoidea* telah dikaji. Kajian dibahagikan kepada lima bahagian iaitu penyiasatan kimia, pemprofilan kimia, pemprofilan biokimia, kajian stabiliti dan pemprofilan biologi.

Lima sebatian telah diasingkan yang merangkumi tiga triterpenoid, β-amyrin sinamat, β-sitosterol dan friedelin dan dua flavonoid, viteksin dan isoviteksin. Pengecaman dan penjelasan struktur sebatian-sebatian ini dibangunkan melalui teknik spektroskopi.

Ekstrak dianalisis untuk penentuan flavonoid total, polifenol, tanin, protein, polisakarida dan glikosaponin. Kandungan flavonoid total, polifenol dan tanin dalam ekstrak-ekstrak ini dalam julat 27.35 ± 1.08 sehingga 86.85 ± 0.58 (mg/g), 36.37 ± 0.27 sehingga 172.78 ± 0.47 (mg/g) dan 96.32 ± 0.75 sehingga 942.15 ± 4.08 (mg/g), masing-masing. Peratus protein, polisakarida dan glikosaponin total dalam ekstrak-ekstrak ini dalam julat 63.39 ± 0.26 sehingga 66.53 ± 2.74 (%), 0.01 ± 0.00 sehingga 5.11 ± 0.17 (%) dan 7.44 ± 1.07 sehingga 35.21 ± 1.26 (%), masing-masing.

Pemprofilan kimia kualitatif dan kuantitatif melibatkan penggunaan UV, FTIR, HPTLC dan HPLC. Sistem HPLC cerunan (gradient) telah dibangunkan dan divalidasi menggunakan viteksin dan isoviteksin sebagai penanda dan telah

digunakan untuk kuantifikasi penanda tersebut dalam ekstrak metanol dan air. Kepekatan viteksin dalam ekstrak metanol dalam julat 4.95 sehingga 12.18 mg/g, sementara kepekatan viteksin dalam ekstrak air dalam julat 2.48 sehingga 19.05 mg/g. Kepekatan isoviteksin dalam ekstrak metanol dalam julat 1.58 sehingga 41.49 mg/g, sementara kepekatan isoviteksin dalam ekstrak air dalam julat 3.61 sehingga 26.94 mg/g.

Kajian pemprofilan biokimia ekstrak daun diselidiki untuk penentuan aktiviti antioksidan, antihipertensi, anti-inflamasi dan antiangiogenik. Ekstrak berbagai varieti tumbuhan yang berbeza menunjukkan pelbagai aktiviti antioksidan pada pelbagai model antioksidan seperti penghapusan radikal bebas DPPH, penghapusan anion superoksida, xantina oksidase (XOD), kuasa penurunan Fe (III) ke Fe (II), penghapusan nitrik oksida (NO) dan peroksidasi lipid. Kajian antihipertensi menggunakan asai enzim pengubah angiotensin (ACE) menunjukkan bahawa ekstrak mempunyai potensi sebagai agen antihipertensi. Aktiviti antihipertensi ekstrak ditemui setanding dengan kaptopril, perencat ACE yang diketahui secara meluas. Ekstrak menunjukkan variasi dalam aktiviti anti-inflamasi dalam pelbagai model seperti lipoksigenase (LOX), hialuronidase (HYAase) dan edema telinga dicetus TPA. Dalam kajian antiangiogenik, ekstrak FDLSPLSW dan penanda, viteksin dan isoviteksin menunjukkan aktiviti 100%.

Dalam kajian kestabilan, ekstrak disimpan pada 4 keadaan simpanan yang berbeza selama enam bulan, dan sampel dianalisis dalam selang 1 bulan menggunakan FTIR dan HPLC. Berdasarkan kajian, didapati sebatian penanda dalam ekstrak yang disimpan pada 25 ºC adalah lebih stabil dari ekstrak yang disimpan pada 30 ºC /65% RH, 40 °C /75% RH, 50 °C /85% RH and 60 °C /85% RH. Selain itu, isoviteksin didapati lebih stabil dibandingkan dengan viteksin. Anggaran hayat

simpan (t_{90}) dari viteksin dan isoviteksin adalah sekitar 1.5 dan 14 bulan, masing-masing pada 25 º C.

Dalam kajian farmakokinetik, ekstrak air *FD*. var. *terengganuensis* berlabel FDLSPLS diberikan secara oral dalam dos 500 mg/kg berat badan kepada tikus *Sprague-Dawley*. Sampel plasma, urin dan najis dianalisis dengan menggunakan kaedah HPLC cerunan, yang dibangunkan dan divalidasi menggunakan viteksin dan isoviteksin. Keputusan kajian menunjukkan bahawa kedua-dua penanda tidak dapat dikesan dalam sampel plasma, urin dan najis.

Keputusan kajian menunjukkan bahawa kaedah HPLC yang dibangunkan boleh digunakan untuk pemiawaian ekstrak. Kedua-dua ekstrak telah menunjukkan potensi sebagai agen antioksida, anti-inflamasi dan antihipertensi. Sementara, ekstrak air *FD* var. *terengganuensis* menunjukkan aktiviti antiangiogenik.

PHYTOCHEMICAL, BIOLOGICAL, STABILITY AND PHARMACOKINETIC STUDIES ON THE EXTRACTS OF THREE VARIETIES OF *Ficus deltoidea* Jack. LEAVES

ABSTRACT

This study has been conducted to provide information on the standardization of extracts of *Ficus deltoidea* (*FD*) leaves. Three plant varieties namely *FD* var. *terengganuensis*, *FD* var. *angustifolia* and *FD* var. *deltoidea* were studied. The study was divided into five parts: chemical investigation, chemical profiling, biochemical profiling, stability studies and biological profiling.

Five compounds have been isolated that includes three triterpenoids, β-amyrin cinnamate, β-sitosterol and friedelin and two flavonoids, vitexin and isovitexin. Identification and structural elucidation of these compounds was established through spectroscopic techniques.

The extracts were analysed for the determination of total flavonoids, polyphenols, tannins, protein, polysaccharides and glycosaponin. The total flavonoids, polyphenols and tannins content in these extracts in range 27.35 ± 1.08 to 86.85 ± 0.58 (mg/g), 36.37 ± 0.27 to 172.78 ± 0.47 (mg/g) and 96.32 ± 0.75 to 942.15 ± 4.08 (mg/g), respectively. The percentage of total proteins, polysaccharides and glycosaponins in these extracts in range 63.39 ± 0.26 to 66.53 ± 2.74 (%), 0.01 ± 0.00 to 5.11 ± 0.17 (%) and 7.44 ± 1.07 to 35.21 ± 1.26 (%), respectively.

The qualitative and quantitative chemical profiling involved the use of UV, FTIR, HPTLC and HPLC. A gradient HPLC system has been developed and validated using vitexin and isovitexin as markers and was applied for the quantification of these markers in methanol and water extracts. The concentration of vitexin in

methanol extracts in range 4.95 to 12.18 mg/g, whilst the concentration of vitexin in water extracts in range 2.48 to 19.05 mg/g. The concentration of isovitexin in the methanol extracts in range 1.58 to 41.49 mg/g, while the concentration of isovitexin in the water extracts in range 3.61 to 26.94 mg/g.

Biochemical profiling study of the leaves extracts were investigated for determination of antioxidant, antihypertensive, anti-inflammatory and antiangiogenic activities. The extracts of different varieties of the plant displayed varying antioxidant activities in various antioxidant models such as DPPH free radical scavenging, superoxide anion scavenging, xanthine oxidase (XOD), reducing power of Fe(III) to Fe(II), nitric oxide (NO) scavenging and lipid peroxidation. Antihypertensive studies using angiotensin converting enzyme (ACE) assay showed that the extracts have potential as antihypertensive agents. Antihypertensive activities of the extracts were found to be comparable to captopril, a widely known ACE inhibitor. The extracts showed the variation in the anti-inflammatory activity in various models such as lipoxygenase (LOX), hyaluronidase (HYAase) and TPA-induced ear oedema. In antiangiogenic studies, FDLSPLSW extract and the markers, vitexin and isovitexin showed 100 % activity.

In stability studies, the extracts were stored at 4 different storage conditions for six months, and samples were analysed at an interval of 1 month using FTIR and HPLC. Based on the studies, it was found that marker compounds in the extracts stored at 25 ºC were more stable as compared to the extracts stored at 30 ºC /65% RH, 40 °C /75% RH, 50 °C /85% RH and 60 °C /85% RH. Moreover, isovitexin was found to be more stable as compared to vitexin. Estimated shelf life (t_{90}) of vitexin and isovitexin was approximately 1.5 and 14 month, respectively at 25 ºC.

In pharmacokinetic studies, water extracts of *FD* var. *terengganuensis* labelled FDLSPLS were administered orally in a dose of 500 mg / kg body weight to Sprague-Dawley rats. The plasma, urine and feces samples were analysed using gradient HPLC method, which was developed and validated using vitexin and isovitexin. Results of the study show that both the markers were not detected in plasma, urine and feces samples.

Results of the study indicate that the developed HPLC methods can be applied for standardization of the extracts. Both extracts have shown potential as an antioxidant, antiinflammatory and antihypertensive agent. Whilst, the water extract of *FD* var. *terengganuensis* show antiangiogenic activity.

CHAPTER ONE

INTRODUCTION

1.1 Introduction

Medicinal plants have been used for thousands of years in virtually all cultures as sources of medicine. Over recent years, the use of medicinal plants has grown significantly. This is not only due to a general trend toward the use of natural products, but more towards available evidence regarding the safety and efficacy of herbal medicinal products. In most of the European countries, submissions of quality, safety and therapeutic data is mandatory for authorization of herbal medicinal products. Germany, France, Sweden, Denmark and Switzerland have also established specific national regulations on evaluation of herbal products. Other countries like Netherland, United Kingdom and Portugal regulate these products in the same way as ordinary pharmaceuticals (Busse, 2000).

According to the World Health Organization (WHO), herbal medicines contain plant parts or plant material in the crude or processed state as active ingredients and may contain excipients. Combinations with chemically defined active substances or isolated constituents are not considered herbal medicines (WHO Technical Report, 1996). Similarly, the European Medicinal Evaluation Agency (EMEA) defines herbal medicinal products as medicinal products containing exclusively herbal drugs or herbal drug preparations.

Herbal drugs are plants or plant parts in an unprocessed state which are used for medicinal or pharmaceutical purpose. Herbal drugs preparation are comminuted or powdered herbs, extracts, tinctures, fatty or essential oils, expressed juices, processed resins or gums, and so forth prepared from herbal drugs, and

preparations whose production involves a fractionation, purification or concentration processes (EMEA, 1999).

Herbs contain complicated mixture of organic chemicals which may include fatty acids, sterols, alkaloids, glycosides, saponins, tannins and terpenes. The concentration of these substances depends on various factors related to the species variation, seedlings growing condition, processing and production of the herbal products.

Herbal products may contain a single herb or combinations of several herbs believed to have complementary effects. But it is usually difficult to determine which components are biologically active. The chemical constituents in the herbs were affected by the processing activity and environmental factors that will contribute in their pharmacological effect and the uniformity of the herbal products. To overcome this situation, manufacturers have attempted to create more consistent products through standardization using marker compounds, unique chemical constituents in the herbs and alter the production process to achieve consistent level of the markers in every batch.

Herbal products are usually perceived as safe because they are natural. However, many side effects have been reported from the use of herbal products (Bent and Ko, 2004). These include direct toxic effects and allergic reactions. The information on safety and efficacy of herbs or plant medicine are limited in a number of ways such as data is year's old, limited *in vitro* and *in vivo* studies, drug interactions, effects in special populations and toxic reactions (O'hara *et al*., 1998). The Food and Drug Administration (FDA) has categorized about 250 herbs as "generally recognized safe" (GRAS) including chamomile, echinacea, feverfew, garlic, ginger, ginkgo and

ginseng; based on their long-term traditional use without significant side effects (O'hara *et al*., 1998).

For the purpose of lead discovery or for the scientific validation of a traditional medicinal plant or a phytopharmaceutical, active principles in the complex matrices need to be identified. It is currently estimated at least 420,000 plants species exist in nature (Bramwell, 2002), less than 5% of the plants have been screened for one or more biological activities (Verpoorte *et al*., 2000). More than 100,000 secondary metabolites are known though only a small percentage of all plant have been studied.

It is estimated about 25% of all the modern medicines are directly or indirectly derived from higher plants. For antitumor and antimicrobial drugs, about 60% of the medicines available in the market are derived from natural products, mainly from the higher plants (Farnsworth and Morris, 1976; de Smet, 1997; Cragg *et al*., 1998, Shu, 1998; Calixto, 2000). According to the World Health Organization, about 65-80% of the world's population which lives in developing countries depends on the medicinal plants for primary healthcare due to lack of access to modern medicine (Calixto, 2000). In developed countries such as Germany, France, Italy and the United States, herbal medicinal preparations are very popular and have been used traditionally for a longtime and there are guidelines for the registration of such medicines (Calixto, 2000).

Based on the WHO and the EMEA quality guidelines (Table 1.1), the great efforts have to be made to ensure the quality of the herbal drugs. To ensure a consistent quality of a therapeutic agent, it is evident that only suitable standardized and validated process should be used. In addition, fingerprint, chromatograms and spectrograms analysis can also provide chemical information to help in

standardization. This technique is more effective for comparing and evaluating quality control of herbal drugs (Ren, 2001 and Li *et al*., 2002 as cited by Chaudhary *et al*., 2007).

Table 1.1: WHO Research Guidelines for Evaluating the Safety and Efficacy of Herbal Medicine (WHO, 1993)

• To ensure the reliability and repeatability of research on herbal medicines, the identity and quality of the plant material or preparation must be determined.
• A description should be provided of the physical and chemical tests done to identify the plant substances and a chromatogram of the active fraction or characterizing compound should be sufficient to identify a characteristic mixture of substances.

1.2 Quality Control in the Standardization of Herbal Medicine

Herbal medicines are formulated from a single or mixture of plants and have been used widely in treating a range of diseases. However, as stated in the Calixto (2000), only few programs have been established to study the safety and efficacy of herbal medicines as originally proposed by the WHO guidelines for the assessment of herbal medicines. Generally, herbal medicines are always assumed safe and free from side effects based on their traditional use. Although this is not supported by scientific data, the situation leads to the tremendous growth in phytopharmaceutical usage as compared to synthetic drugs (Calixto, 2000).

Many phytopharmaceuticals in the market are crude extracts and thus complex mixtures of compounds. Investigation of pharmacological activity on single isolated compounds versus the original plant extracts exerts polyvalent pharmacological effects (Wagner, 2001). This might explain the pharmacological synergistic effects and the phenomenon that very often an extract possesses a much better therapeutic

effect than single isolated constituent. In consequence, the application of refined herbal extract rather than “isolated active principle(s)” may be favored in order to get benefit from the broad therapeutical and pharmacological action related to the special composition of the ingredients in the entire plant.

Herbal medicinal products (HMPs) consist of hundreds of constituents and some of them may be very toxic such as digitalis, pyrrolizidine alkaloids, ephedrine and phorbol esters. Establishing appropriate strategies for the analysis of quality, safety and efficacy, and the process of standardization of HMPs is a big challenge due to complex chemical composition. With increasing knowledge and advances in analytical methods, standardized, safe and high quality HMPs can be manufactured successfully.

In this study, *Ficus deltoidea* (*FD*) which is locally known as ‘mas cotek or secotek emas’ has been selected. It is one of the most popular medicinal plants after Tongkat Ali (*Eurycoma longifolia* Jack), Hempedu bumi (*Andrographis paniculata*), Misai Kucing (*Orthosiphon stamineus*), Kacip Fatimah (*Labisia pumila*) and pegaga (*Centella asiatica*) because of its traditional use in treating many disease including high blood pressure, improve blood circulation, diabetes, gout, pneumonia, heart problems, diarrhea and skin infection (Fasihudin and Hasmah, 1991).

1.3 Research Objectives

Although, a number of products manufactured from *Ficus deltoidea* are available in the market, there is still lack of information in terms of the chemical components, quality, safety and efficacy of the plant. Since, the plant being one of the popular herbs used in Malay traditional medicine, the pharmacological properties of the plant have not been studied yet.

Objectives of the study are:

1. To identify chemical constituents of *FD* leaves in order to develop and validate a reliable analytical method for chemical profiling and standardization of *FD* leaves extracts.
2. To evaluate *FD* leaves extracts for *in vitro* biological activities such as antioxidant, anti-inflammatory, antihypertensive and antiangiogenesis.
3. To investigate the *FD* leaves extracts for accelerated stability.
4. To investigate the pharmacokinetics of selected *FD* leaves extracts in rats.

CHAPTER TWO

TAXONOMIC CLASSIFICATION AND LITERATURE REVIEW

2.1 Taxonomic Classification

Taxonomically, this plant is classified as the following scheme:

Family	:	Moraceae
Genus	:	*Ficus*
Species	:	*deltoidea*
Scientific name	:	*Ficus deltoidea* Jack
Synonyms	:	*Ficus diversifolia* Blume

2.1.1 Vernacular Name

In Peninsular Malaysia, East Malaysia and Kalimantan, this plant is known as mas cotek, secotek emas, telinga kera, sempit-sempit and agoluran. In Indonesia, it is known as tabat barito, ara jelatih, ara tunggal, api-api telinga gajah and api-api-telinga kera and in Africa, kangkalibang.

2.1.2 Nomenclature

The common name of this plant comes from the habit of as epiphytes on larger trees. The scientific name, deltoidea or triangularis refers to the shape of the leaves. Same is in Malaysia, the local name of this plant referred to the golden dot (emas or mas) which can be observed on the upper layer of the leaves. Also the shape of the leaves was slightly same as the ear of monkey or ‘beruk or kera’ in Malay.

2.1.3 Moraceae

According to the Bhattacharya and Johri (1998) in their book title *Flowering Plants; Taxonomy and Phylogeny*, the family of Moraceae consists of 53 genera and 1400 species, distributed in tropical and subtropical zones of the world (Africa, Asia and

America). They also have stated that genus *Ficus* has more than 1000 species and their statement has been proved by Wagner *et al*. (1999) as cited by Starr *et al*. (2003).

The genus *Ficus* occupies many habitats from lowland swamps to mountain rainforest and semi-arid areas. They have a wide range of life forms from lianescent climbers to hemiepiphytes and forest canopy trees.

2.1.4 Plant Description

Ficus deltoidea (FD) Jack is evergreen shrub or small tree up to 2 m tall, usually bushy and sometimes epiphytic. Leaves of this species are broadly spoon-shaped to obovate, blade thinly to thickly leathery, 2-8 x 1.5-7.5 cm, bright green above and rust-red to olive brown beneath. The underside of the leaf showed midrib forked or not but generally there is a black spot (gland) at the fork and on the upper side of the leaves, yellow spot can be observed all over the surface.

The shapes of the leaf are more variable in the whole genus and ranges from elliptical or spathulate-shaped, the apex is blunt, truncate or widely notched and rarely pointed. The leaves are also succulent. Shapes of the figs also vary from one another, from spherical to round: peduncle 3-15 x 1-2 mm: basal bract ca. 1 mm: body 5-7 mm wide and with 1.5 cm across. Figs are freely produced in pairs and ripening from dull yellow and then to orange or red. This plant is native to South East Asia, Borneo and Philippines (Brickell and Zuk, 1997 cited by Starr *et al*. 2003). Riffle (1998) cited by Starr *et al*. (2003) described this specie as indigenous to the Southern Philippines southward and westward to South East Asia, Malaysia and Indonesia.

According to the Malaysian traditional herbalist, at least 7 different varieties are identified, which are FD var. *motleyana,* FD var. *angustifolia,* FD var. *intermedia,* FD var. *kunstleri*, FD var. *deltoidea* , FD var. *bilobata* and FD var. *terengganuensis* (Kamarudin and Latiff, 2002). Other varieties also have been identified by Corner, 1965 and 1969; FD var. *angustissima*, FD var*. arenaria*, FD var*. bilobata*, FD var*. borneensis*, FD var*. kinabaluensis*, FD var*. lutescens*, FD var*. oligoneura* and FD var*. peltata.*

For the purpose of analytical study, three varieties have been selected which are FD var. *angustifolia,* FD var*. terengganuensis* and FD var. *deltoidea* because availability of species during the study conducted (Figure 2.1).

2.1.4 (a) FD var. *terengganuensis* (Corner, 1969)

Distribution: Malaya (Terengganu, east coast of Pahang)

Ecology: Coastal shrub and in Leptospermum forest at 1300 m altitude, also epiphytic in lowland forest.

Morphology: Lamina size from 2.3 x 1.8 – 5.5 cm, elliptic to rounded-obovate or some what bilobed: midrib dichotomous about 1/2-2/3 lamina; glands 3-4 (-5), two basal, the others at the dichotomies of the main veins: petiole 10-50 x 1-2 mm. Fig-body 9-12 mm wide, rose-red to purple-black when ripening: peduncle 6-20 x 1.5 mm: basal bracts 1-1.5 mm. Twigs are 2 mm thick.

2.1.4 (b) FD var. *angustifolia* (Corner, 1969)

Distrbution: Lower Thailand, Malaya, Riau Archipelago, Sumatra, Borneo, Anamba and Natuna Island, Palawan.

Ecology: Epiphytic in lowland and mountain forest up to 1500 m altitude and common on seashores

Morphology: A shrub, growing up to 4 m high. Shapes of this varieties are spathulate or lanceolate obovate, rarely obscure lobed at the apex and sizes from 2-7 cm x 0.8-3 cm. There also a midrib dichotomous at or above the middle of the leaf. At the lower part, one gland can be seen at the fork of the midrib. Fig ripening yellow to orange or red: peduncle 5-15 x 1 mm, slender: body 6-8 x 4-6 mm.

2.1.4 (c) FD var. *deltoidea* (Corner, 1969)

Distribution: Malaya (Singapore, East Johore, South East Pahang), Riouw and Lingga Archipelagos, Bangka, Sumatra, Borneo.

Ecology: Generally epiphytic in lowland and mountain forest, up to 1200 m altitude (Kinabalu), also terrestrial on rocks and sea-shores.

Morphology: A small shrub with smaller figs ripening orange to red. The leaves are lanceolate and penniveined. A strong distinction of this plant is rugose-angular ovary.

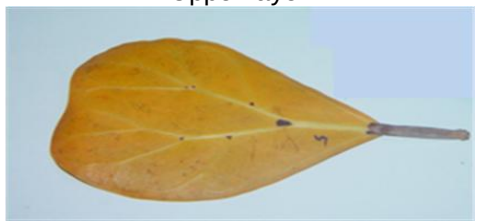
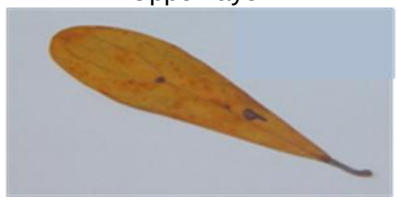
Ficus deltoidea var. *terengganuensis*	*Ficus deltoidea* var. *angustifolia*	*Ficus deltoidea* var. *deltoidea*
		
 Upper layer	 Upper layer	 Upper layer
 Lower layer	 Lower layer	 Lower layer

Figure 2.1: Pictures of the plants

2.1.5 Traditional Uses

In Malaysia, decoction of the *Ficus deltoidea* leaves is used to improve blood circulation and regain body strength and for treating diabetes, high blood pressure, heart problems, gout, diarrhea, pneumonia and skin infection. Some communities in Sabah consume the plant leaves as herbal tea for anti aging and youthful appearance (Fasihudin and Hasmah, 1991).

There are many claims by the traditional medicine practitioners regarding this plant in Malaysia. Unfortunately, there is no scientific study on this plant to prove these claims. Therefore, leaves of this plant were selected in this study to provide information to the herbal industry in Malaysia so that they can produce high quality products.

2.2 Literature Review

Until now only two report of blood glucose lowering effect and antinociceptive effect of *Ficus deltoidea* have been published (Sulaiman *et al*., 2004; Sulaiman *et al*., 2008). Phytochemical screening detected the presence of different classes of constituents, such as flavonoids, saponins, steroids, terpenes and tannins (Sulaiman *et al*., 2008). Therefore, the studies have been conducted to give the information on the safety, quality and efficacy aspects of *Ficus deltoidea* leaves.

The traditional uses and scientific studies on genus *Ficus* are given in Table 2.1 and Table 2.2, respectively. From the aerial part of genus *Ficus* various chemical constituents including phenolics, triterpenoids, sterols, flavonoids and alkaloids has been identified. Reviews on the chemicals isolated from genus of *Ficus* are summarized in Table 2.3.

2.2.1 Traditional Uses of the Genus of *Ficus*

Table 2.1: Traditional uses of the genus of *Ficus*

Ficus spp.	Traditional uses	References
Ficus platyphylla	• In Northern Nigeria, this plants is used for treating several diseases including insomnia, psychorosis, depression and also used as an analgesic	Audu (1989) as cited by Chindo *et al.*, 2003.
Ficus racemosa (*Ficus glomerata*)	• In India the leaves of this species has been used for treating dysentery, bilious affection and also used as a mouth wash in spongy gum. • The roots, fruits and bark are used for treating dysentery and diabetes. • The fruits are also used to relieve diarrhoea • In Bombay, this plant is a popular remedy for mumps and other inflammatory enlargement and the milky juice is popular among traditional healers as an antiinflammatory remedy. • Also reports for treatment of skeletal fracture • The roots are used as medicine against hydrophobia. Its fruits are effective against leprosy, diseases of the blood, fatigue, bleeding nose and cough. Its bark used for asthma and its leaves for bronchitis. It is also used as carminative, astringent, vermifuge and anti-dysentery drug. The plant also used to relieve inflammation of skin wounds, lymphadenitis, sprains and fibrositis.	Mandal *et. al*, 2000a; Kirtikar and Basu, 1975; Nadkarni *et al.*, 1996; Chopra *et al.*, 1985; Ekanayake (1980) as cited by Mandal *et al.*, 2000a Mandal *et al*., 2000b
Ficus hispida	• Various parts of this plant are used in Indian traditional medicine for the treatment of various ailments. Bark was used as emetic and anti-diarrhoeal. Fruits used as tonic, lactogogue, cooling, astringent and in hepatic obstruction. • The plant was found to be used widely as an anti-diarrhoeal, hepatoprotective, antitussive, antipyretic, anti-inlammatory, depurative, vulnerary, hemostatic, anti-ulcer and in treatment of anemia. • In West Bengal, India, people of Khatra used the leaves of this plant to cure diarrhoea.	Kirtikar and Basu, 1956; Nadkarni, 1976; Rastogi and Mehrotra, 1993; Peraza-Sanchez *et al*., 2002; Anon (1956) and Anon (1986) as cited by Mandal and Ashok Kumar, 2002
Ficus bengalensis	• Leaves of this plant are good for treating ulcers and leprosy. The bark is astringent and useful in the treatment of dysentery, diarrhoea and diabetes. An infusion of the young buds also used for the treatment of diarrhoea and dysentery. The young tips of hanging roots are given for obstinate vomiting. The milky juice is externally applied for pains and bruises and as an anodyne in rheumatism, lumbago and also used as	Satyati *et al*., 1976; Hosamani and Pattanashettar, 2003 Kirtikar and Basu, 1933

	remedy for toothache. • The seeds and fruits are used for cooling and as tonic	
Ficus carica	• Used for prevention of nutritional anaemia and an anthelmintic • Various parts of this plants used by the native of India as a diuretic, demulcent, emollient and as an anthelmintic • Fruits of this plant if taken internally along with senna and carminative herbs can gave mildly laxative properties	Saeed and Sabir, 2002; Sastri, 1976; Jaffe, 1943 Omar *et al*., 2004
Ficus sur	• People of Zulu in Africa drink a decoction of the root and bark for pulmonary tuberculosis, an infusion of the leaf and bark used to improve milk production in cattle. • Tanganyika's people used a decoction of bark as galactogogue in women and cows and to prevent vomiting. • In West Africa, the plant is used by traditional eye doctors. • In Zaire, the latex used for the treatment of burns. • In northern part of Nigeria, fresh young aerial root with the inner bark is chewed with kolanut to alleviate thirst and to treat throat. The leaves are claimed to act as a remedy for pectic ulcer.	Watt and Breyer, 1962 Burkill, 1985 Kunle *et al*., 1999
Ficus septica	• In Papua New Guinea, leaf of this plant is used to cure colds, fever, fungal and bacterial diseases.	Baumgartner *et al*., 1990
Ficus maxima	• In folk medicine this plant has been used as anthelminthic and anti-rheumatic, anti-anaemic and antipyretic agents.	Diaz *et al.*, 1997
Ficus pumila	• The leaves of the plant has been traditionally consumed by some Okinawan elders in Japan either as a beverage or used as an invaluable medicinal herb by the folks to treat diabetes, dizziness, high blood pressure, and neuralgia. There is evidence that some of the compounds in the plants regularly consumed by the Okinawans have powerful antioxidant and positive hormonal effects	Mitsuhashi, 1988; Tobinaga, 1989 and Nakatani, 1992 as cited by Abraham *et al.*, 2008.
Ficus insipida	• The latex leaves and unripe fruits of this species have been used by the natives in Central America to Argentina in treatment of worm diseases. • Used as an anti-anaemic and anti-pyretic	Peckolt (1942) as cited by Amorin *et al.*, 1999; Lopes *et al*., 1993; Diaz *et al.*, 1997
Ficus beecheyana	• This plant was widely distributed in east of Asia, especially in mainland China, Hong Kong, Vietnam and Taiwan. Its rhizomes have been used in folk medicine to the treatment of rheumatism and diabetes and as carminative.	Lee *et al*., 2002

Ficus fistulosa	• In Central and South America the latex of some *Ficus* species has been traditionally used as vermifuge	Hansson *et al.*, 1986
Ficus asperifolia	• The bark infusion of *Ficus asperifolia* is used for washing sores and ulcers and applied to circumcision wounds In Ghana, the rough leaves are used for scraping patches of ringworm before further treatment	Irvine,1961; Abbiw, 1990
Ficus chlamydocarpa and Ficus cordata	• In Cameroon, both plant were used in the treatment of filaris, diarrhoeal infections and tuberculosis. The decoction from the mixture (1:1 w/w) of root bark from *Ficus chlamydocarpa* and stem bark of *Ficus cordata* are used in the treatment of oral infections.	Khabe (2007) as cited by Kuete *et al.*, 2008
Latex of some *Ficus* species	• Latex has been traditionally used as vermifuge in Central and South America • Some Brazilian species (*Ficus glabrata* HBK, *Ficus doliaria* Martius, *Ficus anthelmintica* Martius and *Ficus radula* Humboldt and Bonpland), were introduced into medical practice as a powerful vermifuge • The latex has been identified as active fraction of protein and namely ficin from the studied done on the *Ficus laurifolia*.	Hansson *et al.*, 1986; Peckolt, 1942 as cited by Amorin *et al.*, 1999 Robbins, 1930
Other species	• The stem bark of *Ficus vallis-chaudae* used for the treatment of heart problems • Leaves of *Ficus thonnigii* used for rheumatism	Kone *et al.*, 2004

2.2.2 Scientific Study on the Genus of *Ficus*

Table 2.2: Scientific study on the genus of *Ficus*

Ficus spp.	Bioactivities study	References
Ficus platyphylla	• Studies has been showed this plant possesses antinociceptive, anti-inflammatory and gastrointestinal activities in rodents • Phytochemical analysis revealed the presence of flavonoids, tannins and saponins. • Chindo et al have been evaluated the central nervous system (CNS) activity using methanolic extract. Results from the studies suggest the extract from stem bark contain psychoactive principles that are sedative in nature with possible neuroleptic properties	Amos *et al*., 2001 and 2002 Amos *et al*., 2001 Chindo *et al.,* 2003
Ficus racemosa	• Evaluation on anti-inflammatory on carrageenin, serotonin, histamine and dextran-induced rat hind paw oedema models. Results possessed of significant anti-inflammatory activity. • Studied on hypoglycaemic and antidiarrhoeal have been reported by Mandal et al. (1997a and 1997b) on leaves • The methanol extract of stem bark possesses significant antipyretic effect in the reduction of normal body temperature and yeast-provoked elevated temperature. • The extract of fruit is used in diabetes and leucoderma. The alcoholic extract of the stem bark of the plant possessed antiprotozoal activity against Entamoeba histolytica. It is also used in the treatment of mumps, smallpox, heamaturia and inflammatory conditions. • Studies done by Khan and Sultana have resulted that the extract from this plant is a potent chemopreventive agents and inhibits Fe-NTA induced renal carcinogenesis and oxidative damage response in Wistar rats.	Mandal *et al*., 2000a Mandal *et al*., 1997a and 1997b Rao *et al.*, 2002 Mandal *et al*., 2000b Khan and Sultana, 2005
Ficus hispida	• Studies done by Mandal and Ashok Kumar have been exhibited that methanolic extract of the leaf showed a significant results on the anti-diarrhoeal activity. • The chloroform extract of the leaves and twids showed significant cytotoxic activity against the lung and colon human cancer cell lines.	Mandal and Ashok Kumar, 2002 Peraza-Sanchez *et al*., 2002
Ficus bengalensis	• A water extract of the bark of this plant has been shown to possesses hypoglycemic, hypocholesterolaemic and hypolipidaemic effects • Two compounds isolated from ethanolic extract of the bark on this plant have shown antioxidant properties. • An antioxidant effect of aqueous extract of the bark has been evaluated in hypercholesterolaemic rabbits. Results showed the extract has significant antioxidant effect	Shroti and Aiman, 1960; Vohra and Parasar, 1970; Shukla *et al*. 1994 and 1995 Daniel *et al*., 1998 ; Shukla *et al*., 2004

	• A glucoside isolated from the bark showed more potent hypoglycemic action as compared to crude ethanolic extract and activity was half of tolbutamide • Oral administration of bark extract showed significant antihyperglycemic effects in diabetic rats by raising serum insulin levels or inhibiting insulinase activity in liver and kidney.	Augusti, 1975 Achrekar *et al*., 1991
Ficus carica	• A study hypoglaemic action of an oral fig-leaf decoctions in type-I diabetic patients by Serraclara et al. (1998) showed the total insulin doses given to the patients decreased during the study according to their glycemic profiles. • Investigation on methanolic extracts and five compounds isolated from the leaves exhibited irritant potential on mice ears. • In Amorin et al. (1999), the latex from this species showed of high toxicity and low anthelmintic efficacy and not recommended for the treatment of intestinal helminthiasis as claimed by the practitioner traditional medicine.	Serraclara *et al*., 1998 Saeed and Sabir, 2002 Amorin *et al.*, 1999
Ficus sur	• Studied done by Kunle et al. resulted that hexane, methanol and water extracts showed antiulcer activity and spasmolytic effects. Hot water extract was most effective compare to others. Furthermore all extracts except hexane extract was found t have gastroprotective activity.	Kunle *et al.*, 1999
Ficus septica	• The methanolic extracts of the leaves showed an intense antibacterial and antifungal activity using TLC bioautographic assays against *Penicillium oxalicum, Bacillus subtilis, Micrococcus luteus and Escherhia coli.*	Baumgartner *et al*., 1990
Ficus fistulosa	• Studies on methanol extract on bark and leaves exhibited of antiplasmodial activity • Studies done by Zheng et al. 2002, has successfully isolated a trichothecenes compound namely verrucarin L-acetate and found to have antimalarial activity against *Plasmodium falciparum*.	Tuyen *et al*., 1998 Zhang *et al*., 2002
Ficus sycomorus	• An aqueous extract of stem bark of this plant can be used as analgesic to human and animals. Furthermore the extract also used for the treatment of ailments such as mental illness, wound dressing and diarrhoea. • Studies done by Sandabe et al. (2003) shown this plant has sedative and anticonvulsant effects on rats. • In Sandabe (2002), LD_{50} value gives 720mg/kg indicated of low toxicity and the extract also found to have partial or no inhibition on bacterial growth. • In Sandabe (2006), the extract of this plant shown the inhibitory effects on muscular activity (smooth and skeletal muscle)	Sandabe and Kwari, 2000; Sandabe *et al*., 2003 and Sandabe, 2002 as cited by Sandabe *et al*., 2006. Sandabe *et al*., 2006.
Ficus	• Studied done by Amorin et al. (1999) show the	Amorin *et al*.,

insipida	high degree of toxicity and the low anthelmintic efficacy of the latex from this species. Therefore the use of the products containing this latex in traditional medicine for the treatment of intestinal helminthiasis is not recommended.	1999
Ficus microcarpa	• Methanol extract of bark have showed of antiplatelet activity. • Ao et al, 2008 reveal that the methanol extracts from bark, fruits and leaves of F. microcarpa contained high amounts of phenolic compounds and showed strong antioxidant and antibacterial effects.	Li and Kuo, 1997 Ao *et al*., 2008
Ficus benjamina	• The methanolic extract of the leaves showed significant anti-inflammatory, antinociceptive and antipyretic activities.	Farag, 2005 as cited by Simo *et al.*, 2008
Ficus hispida and Ficus carica	• Anthelmintic study on the latex of these species in NIH mice naturally nfected with the oxyurids *Syphacia obvelata* and *Aspiculuris tetraptera* and cestode *Vampirolepis nana* showed the low anthelmintic efficacy plus the latex show high degree on toxicity. So the latex is not recommended to use in the traditional medicine as claimed. • Study indicates that the ethanolic aqueous extract of dried ripe fruits of *Ficus carica* possesses an antiplatelet and spasmolytic effect. The spasmolytic effect was mediated possibly through K^+_{ATP} channel activation, which explain some of its medicinal uses in hyperactive gut disorders.	Amorin *et al*., 1999 Gilani *et al.*, 2008.
Ficus asperifolia	• Water extract showed a significant dose-dependent effect on the growth of human dermal fibroblast (142BR) at concentration of 50g/ml with 38% growth. Above 50g/ml doses, extract showed cytotoxicity effect. At high concentration of the infusion of the plant, the new cells will be proliferating. Investigation for the effects of hydrogen peroxide induced damage on the fibroblast cell using same extract showed 58% protection against oxidative damage to the fibroblast cells.	Annan and Houghton, 2008
Ficus chlamydocarpa and *Ficus cordata*	• Methanol crude extracts and isolated flavonoids and isoflavonoids from both plants were evaluated for the antibacterial and anticandidal activities. Both extracts and compounds tested showed antimicrobial activity with crude extract from *Ficus cordata* are more active on the tested mycobacteria than that of *Ficus chlamydocarpa*.	Kuete *et al*., 2008
Other species	• Screening on the leaves of *Ficus thonnigii* showed antibacterial activity. • An aqueous extract of *Ficus polita* showed effective inhibition on HIV-1 and HIV-2 replication. • In the experiments using the latex of *Ficus laurifolia* Lamarck suggested that the active fraction was possibly a protein, called ficin.	Kone *et al*., 2004 Ayisi and Nyadedzor, 2003 Robbins, 1930

2.2.3 Chemical Constituents from Genus of *Ficus*

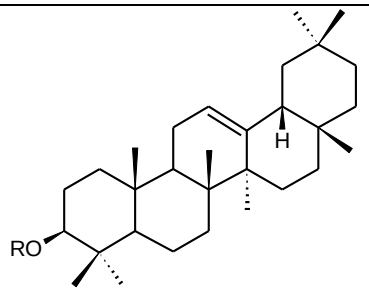
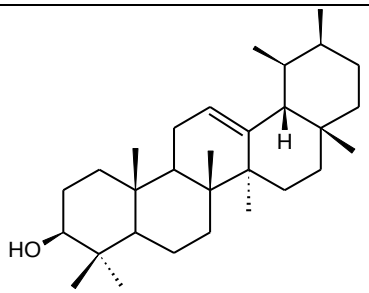
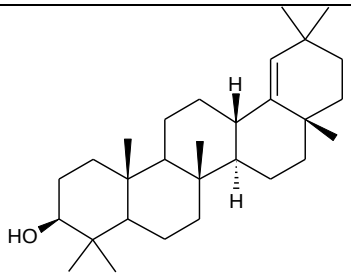
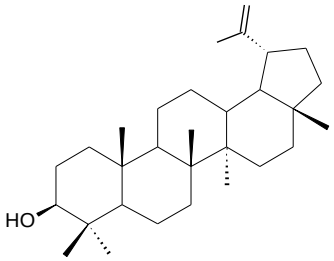
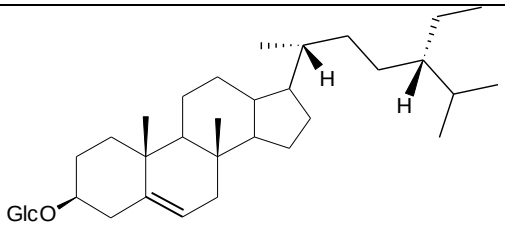
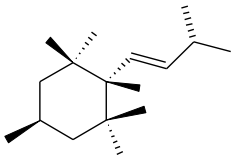
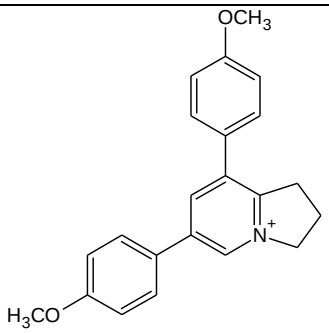
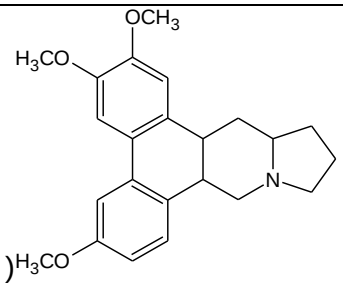
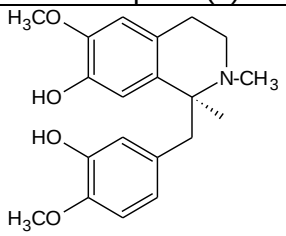
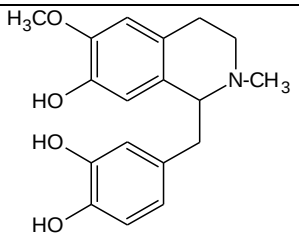
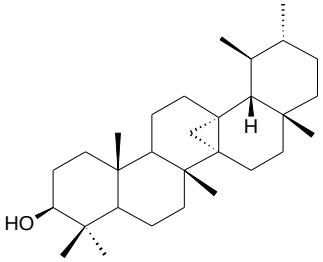
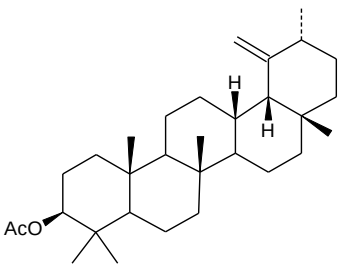
Table 2.3: Chemical constituents from genus of *Ficus*

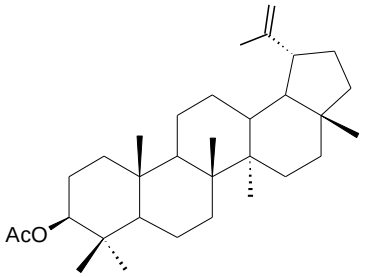
Ficus spp.	Chemical constituents	References
Ficus aripuanensis	β-amyrin (**1**), α-amyrin (**2**), β-amyrin acetate (**3**), Germanicol (**4**), Lupeol (**5**) Sitosterol glycoside (**6**), Aripuanin (**7**)	Nascimento *et al*., 1999
Ficus septica	Ficuseptine (**8**), Antofine (**9**)	Herbert and Moody, 1972; Baumgartner *et al*., 1990
Ficus pachyrachis	(-)-Reticuline (**10**), (+)-Nor-reticuline (**11**)	Khan *et al*., 1992
Ficus carica	Bauerenol (**12**), Calotropenyl acetate (**13**), Lupeol acetate (**14**), Methyl maslinate (**15**), Oleanolic acid (**16**), Ψ-taraxasterol (**17**), Cadelene (**18**), β-amyrin (**1**), Lupeol (**5**), Rutin (**19**), 24-methylenecycloartanol (**20**)	Ahmad and Abdul Malik 1988; Saeed and Sabir, 2002; Abu Mustafa *et al*., 1964; Subramaniam and Nair, 1970; El-Kholy and Shaban, 1966; Ahmad and Abdul Malik, 1988
Ficus maxima	5,7,3',4',5'-pentamethoxyflavone (**21**), 5,6,7,5'-tetramethoxy-3',4'-methylenedioxyflavone (**22**), 5,6,7,3',4',5'-hexamethoxyflavone (**23**), 5,6,7,3',5-pentamethoxy-4'-prenyloxyflavone (**24**)	Diaz *et al.*, 1997
Ficus pumila	Bergapten (**25**), β-sitosterol (**26**), α-amyrin (**1**), Taraxasterol (**17**), 11α-hydroxy-β-amyrin (**27**), Scopoletin (**28**) 7,4'-dimethoxy-5-hydroxyisoflavone (**29**), Genistein (**30**), 5,7,2',5'-tetrahydoxyflavanone (**31**), Naringenin (**32**), Hesperitin (**33**) , Apigenin (**34**) Taxifolin (**35**), Tricetin (**36**), Luteolin (**37**), Chrysin (**38**), Rutin (**19**), Isorhamnetin-3-O-glucoside (**39**), Oxypeucedanin hydrate (**40**), Astragalin (**41**), Isoquercitrin (**42**), Apigenin 6-C-α-L-rhamnopyranosyl-(1—2)-β—D-glucopyranoside (**43**), Kaempferol 3-O-α-L-rhamnopyranosyl (1—6)-β-D-glucopyranoside (**44**), Kaempferol 3-O-α-L-rhamnopyranosyl (1—6)-β-D-galactopyranoside (**45**)	Juan *et al*., 1997, Pistelli *et al*., 2000, Kitajama *et al.*, 1998a and 1998b, Abraham *et al.*, 2008
Ficus altissisma	Demethyl-meliternin (**46**), Scutellarein tetramethyl ether (**47**), Quercetagetin-3,6,7,3',4'-pentmethyl ether (**48**), Myricetin hexamethyl ether (**49**), Demethyl-melibentin (**50**), Hypolaetin pentamethyl ether (**51**)	Mohamed *et al*., 2000
Ficus bengalensis	Rutin (**19**), Quercetin 3-galactoside (**52**), Ψ-taraxasteryl ester (**53**) Studies on the fatty acids in seed oil *of Ficus bengalensis* was found to contain: Vernolic acid (**54**), Malvalic acid (**55**),	Subramaniam and Nair,1970 Subramaniam and Nair, 1970 Hosamani and

	Sterculic acid (**56**), Lauric acid (**57**), Myristic acid (**58**), Palmitic cid (**59**), Stearic acid (**60**), Oleic acid (**61**), Linoleic acid (**62**), Linolenic acid (**63**)	Pattanashettar, 2003
Ficus fistulosa	3b-acetyl22,23,24,25,26,27-hexanordamaran-20-one (**64**), 24-methylenecycloartenol (**65**), Sorghumol (isoarbinol) (**66**), 11a,12a-oxidotaraxeryl acetate (**67**), Ursa-9(11):12-dien-3b-ol-acetate (**68**), 3b-acetyl ursa-14:15-en-16-one (**69**), Lanosterol-11-one acetate (**70**), Verrucarin L acetate (**71**)	Tuyen *et al*., 1998; Zhang *et al*., 2002
Ficus microcarpa	Ficuisoflavone (**72**), Isolupinisoflavone E (**73**), Ficusic acid (**74**), Methyl-4'-hydroxy-3'-methoxytropate (ficusol) (**75**), Ficuglucoside (**76**), 20-taraxastene-3β,22α-diol (**77**), 3β-acetoxy-20-taraxasten-22α-ol (**78**), 3β-acetoxy-22α-methoxy-20-taraxastene (**79**), 3β-acetoxy-20 α,21α -epoxytaraxastane-22α-ol (**80**), 3β-acetoxy-20α,21α-epoxytaraxastane (**81**), 3β-acetoxy-19α-methoxy-20-taraxastene (**82**), 3β-acetoxy-19α-hydroperoxy-20-taraxastene (**83**), 3β-acetoxy-12β,13β-epoxy-11α-hydroperoxyursane (**84**), 3β-acetoxy-11α-hydroperoxy-13α*H*-ursan-12-one (**85**), 3β-acetoxy-1β,11α-epidioxy-12-ursene (**86**), (20S)-3β-acetoxylupan-29-oic acid (**87**), (20S)-3β-acetoxy-20-hydroperoxy-30-norlupane (**88**), 3β-acetoxy-18α-hydroperoxy-12-oleanen-11-one (**89**), 3β-acetoxy-12-oleanen-11-one (**90**), 3β-acetoxy-12,19-dioxo-13(18)-oleanene (**91**), 3β-acetoxy-19(29)-taraxastene-20α–ol (**92**), 3β-acetoxy-21α,22α-epoxytaraxastan-20α-ol (**93**), 3,22-dioxo-20-taraxastene (**94**), 3β-acetoxy-11α,12α-epoxy-16-oxo-14-taraxerene (**95**), 3β-acetoxy-11α,12α-epoxy-14-taraxerene (**96**), 3β-acetoxy-25-methoxylanosta-8,23-diene (**97**), 3β-acetoxy-25-hydroxylanosta-8,23-diene (**98**), Acetylbetulinic acid (**99**), Betulonic acid (**100**), Acetylursolic acid (**101**) Ursonic acid (**102**), Ursolic acid (**103**) 3-oxofriedelan-28-oic acid (**104**), Oleanonic acid (**105**), α-tocospiro A (**106**), α-tocospiro B (**107**), α-tocopherol (**108**), 27-*nor*-3β-hydroxy-25-oxocyloartane (**109**), (22*E*)-25,26,27-*trinor*-3β-hydroxycycloart-22-en-24-al (**110**), 3β-acetoxy-5α-hydroxy-13,27-cyclours-11-ene (**111**), 3β-acetoxy-2α-formyloxy-13,27-cycloursan-11α-ol (**112**)	Li and Kuo, 1997; Li and Kuo, 1998; Chiang and Kuo, 2000; Chiang and Kuo, 2001; Chiang *et al*., 2005; Chiang and Kuo, 2003; Chiang *et al*., 2001
Ficus insipida	Moretenolactone (**113**)	Lopes *et al.*, 1993
Ficus pantoniana	Ficine (**114**), Isoficine (**115**)	John and Russel (1965)

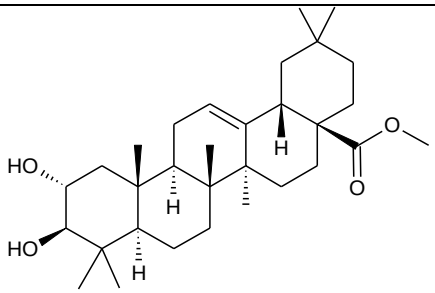
Ficus hispida	Ficustriol (**116**), o-methyltylophorinidine (**117**)	Peraza-sanchez *et al*., 2002
Ficus beecheyana	Threo-2,3-bis(4-hydroxy-3-methoxyphenyl)-3-ethoxyprpan-1-ol (**118**), Erythro-2,3-bis(4-hydroxy-3-methoxyphenyl)-3-ethoxypropan-1-ol (**119**), Erythro-2,3-bis(4-acetoxy-3-methoxyphenyl)-3-ethoxypropan-1-ol acetate (**120**), trans-4,5-bis(4-hydroxy-3-methoxyphenyl)-1,3-dioxacyclohexane (**121**), trans-4,5-bis(4-acetocy-3-methoxyphenyl)-1,3-dioxacyclohexane (**122**), Threo-3-(4-hydroxy-3,5-dimethoxyphenyl)-3-ethoxypropane-1,2-diol (**123**), 2,3-dihydroxy-1-(4-hydroxy-3,5-diemthoxyphenyl)-1-propanone (**124**), 3-hydroxy-1-(4-hydroxy-3,5-dimethoxyphenyl)-1-propanone (**125**)	Lee *et al*., 2002
Ficus infectoria	Luteolin 6-O-β-D-glycopyranoside 3'-O-α-L-rhamnoside (**126**)	Neeru *et al*., 1990
Ficus chlamydo-carpa	β-amyrin (**1**), luteolin (**37**), alpinium isoflavone (**127**), genistein (**30**), laburnetin (**128**), β-sitosterol-3-O-β-D-glucopyranos*ide* (**129**)	Kuete *et al*., 2008
Ficus cordata	β-amyrin (**1**), catechin (**130**), epiafzelechin (**131**), β-sitosterol-3-O-β-D-glucopyranoside (**129**)	Kuete *et al*., 2008
Fcus benjamina	B-amyrin (**1**), β-amyrin acetate (**3**), lupeol (**5**), *β*-sitosterol glucoside (**6**), rutin (**19**), naringenin (**32**), psoralen (**132**), quercetin (**133**), morin (**134**) emodin (**135**), D-mannitol (**136**), cinnamic acid (**137**), caffeic acid (**138**), lactose (**139**), sucrose (**140**), betulinic acid (**141**), platanic acid (**142**), stigmasterol (**143**), benjaminamide (**144**)	Simo *et al*., 2008; Dafalla, 2002

Number in brackets indicates the number of the structure.

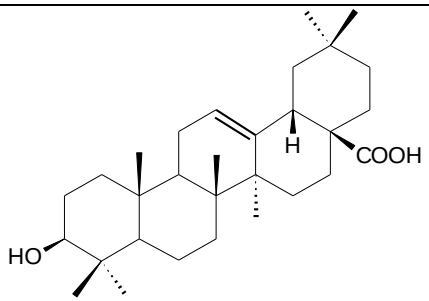
 R: H, β-amyrin (**1**) R: Ac, β-amyrin acetate (**2**)	 α-amyrin (**3**)
 Germanicol (**4**)	 Lupeol (**5**)
 Sitosterol glucoside (**6**)	 Aripuanin (**7**)
 Ficuseptine (**8**)	 Antofine (**9**
 Reticuline (**10**)	 Nor-reticuline (**11**)
 Bauerenol (**12**)	 Calotropenyl acetate (**13**)



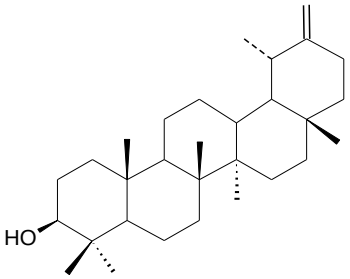
Lupeol acetate (**14**)



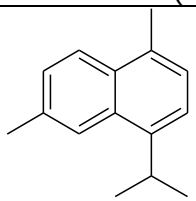
Methyl maslinate (**15**)



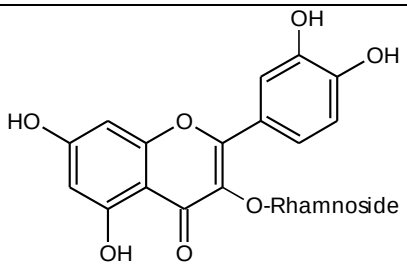
Oleanolic acid (**16**)



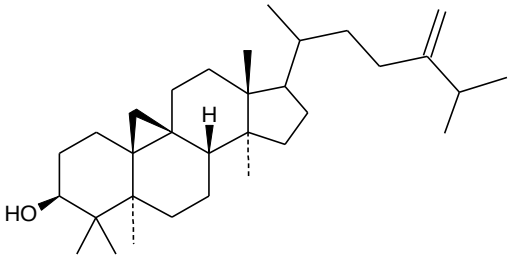
Ψ-taraxasterol (**17**)



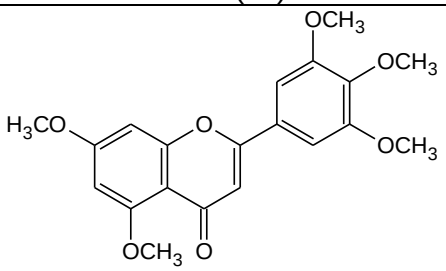
Cadalene (**18**)



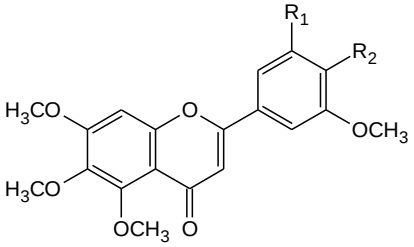
Rutin (**19**)



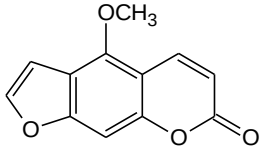
24-methylenecycloartanol (**20**)



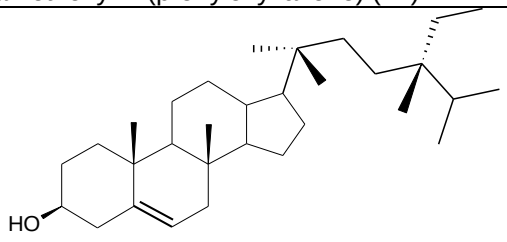
5,7,3’,4’,5’-pentamethoxyflavone (**21**)



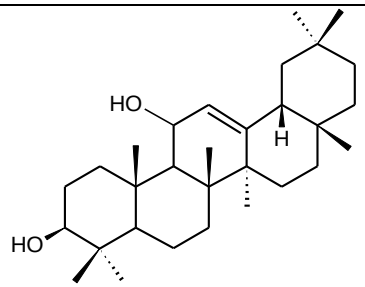
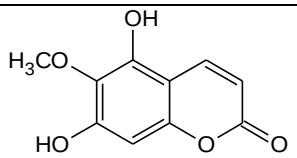
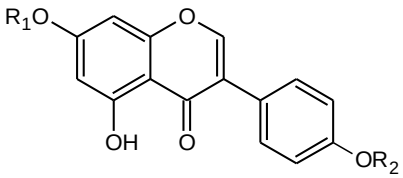
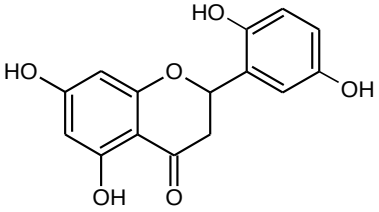
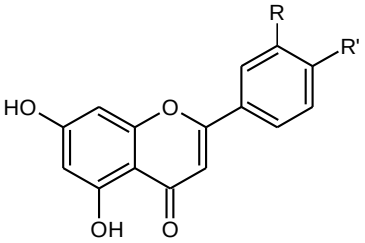
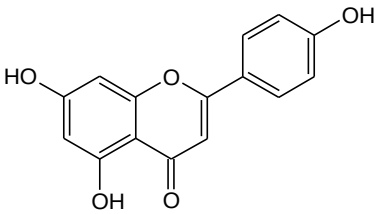
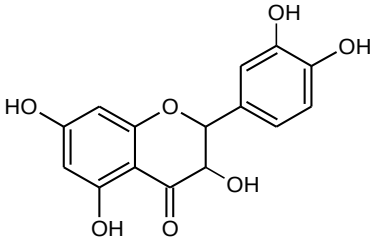
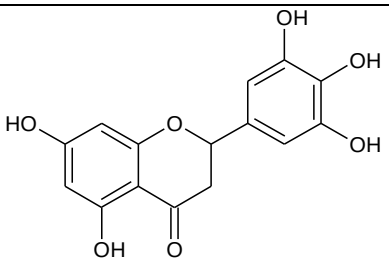
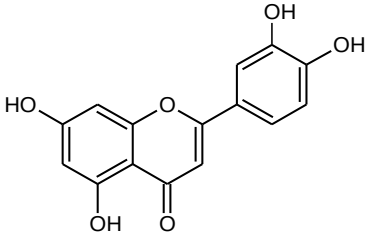
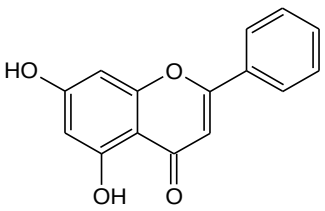
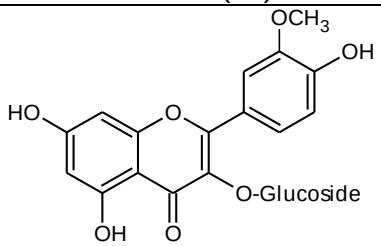
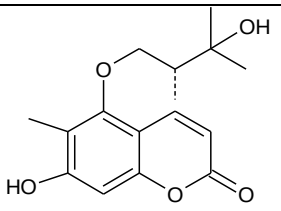
R_1+R_2 OCH_2O; 5,6,7,5'-tetramethoxy-3',4'-methylenedioxyflavone (**22**)
R_1=R_2 = OCH_3; 5,6,7,3',4',5'-hexamethoxyflavone (**23**)
R_1= OCH_3, R_2= $OCH_2CH=CH_2$; 5,6,7,3',5'-pentamethoxy-4'-(prenyloxyflavone) (**24**)

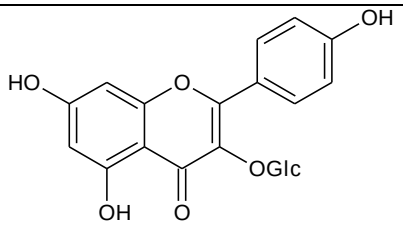


Bergapten (**25**)

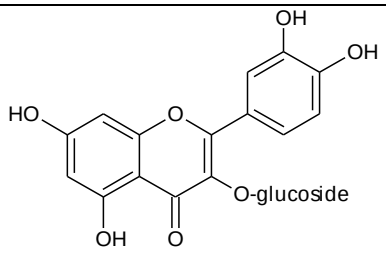


β-sitosterol (**26**)

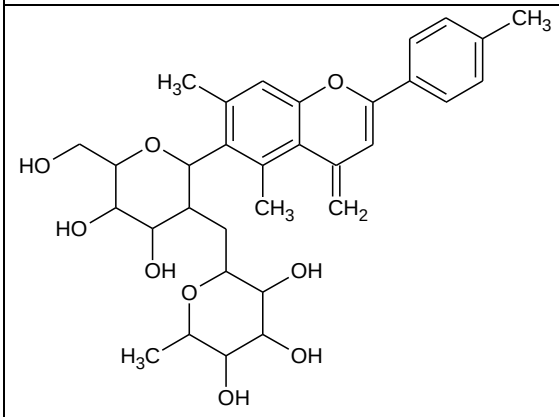
 11α-hydroxy-β-amyrin (**27**)	 Scopoletin (**28**)
 R_1=R_2= OCH_3; 7,4'-dimethoxy-5-hydroxyisoflavone (**29**) R_1=R_2= OH; genistein (**30**)	 5,7,2',5'-tetrahydoxyflavanone (**31**)
 R = H; R' = OH, Naringenin (**32**) R = OH; R' = OCH_3, Hesperitin (**33**)	 Apigenin (**34**)
 Taxifolin (**35**)	 Tricetin (**36**)
 Luteolin (**37**)	 Chrysin (**38**)
 Isorhamnetin-3-O-glucoside (**39**)	 Oxypeucedanin hydrate (**40**)



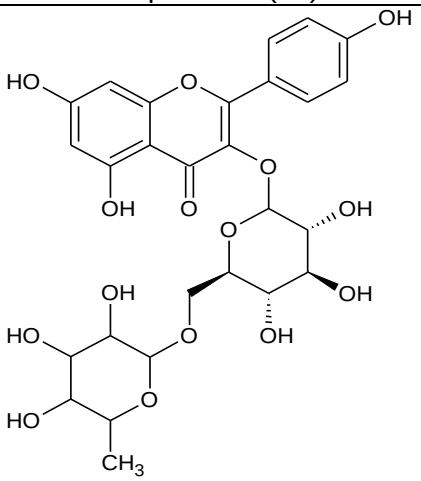
Astragalin (**41**)



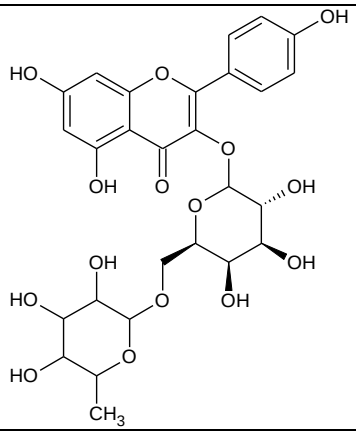
Isoquercitrin (**42**)



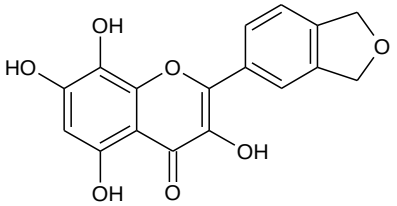
apigenin 6-C-α-L-rhamnopyranosyl-(1—2)-β—D-glucopyranoside (**43**)



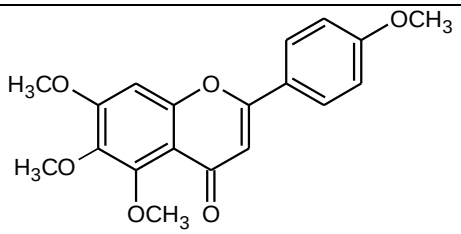
kaempferol 3-O-α-L-rhamnopyranosyl (1—6)-β-D- glucopyranoside (**44**)



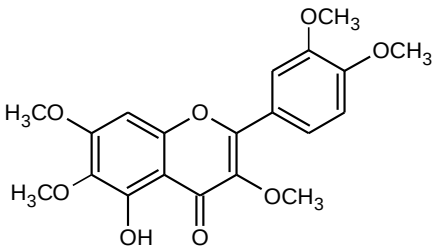
kaempferol 3-O-α-L-rhamnopyranosyl (1—6)-β-D-galactopyranoside (**45**)



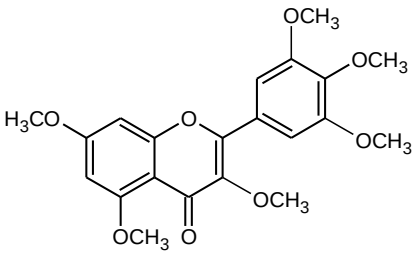
Demethyl-meliternin (**46)**



Scutellarein tetramethyl ether (**47**)



Quercetagetin-3,6,7,3',4'-pentmethyl ether (**48**)



Myricetin hexamethyl ether (**49**)