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ABSTRACT

Plants have played an important role in the ancient culture of India, China and Egypt as medicine. Plants have been and always will be an important source of new drugs and new drug leads. Drug discovery based on plants have resulted in the development of anticancer agents and continues to contribute to new leads in clinical trials. The discovery of Cinchona in the 17th century, followed by Digitalis, morphine and then the introduction of synthetic aspirin, a derivative of a plant-based drug, have led human beings to believe in the many wonders of the wealth of the forests. Natural products have provided challenging synthetic targets and their biological activity has given leads for the development of valuable medicines. Screening programmes exist for bioactive compounds and these have led to new drugs, example: taxol - which is used for the treatment of various cancers. Natural products also play a role in ecology by regulating the interactions between plants, microorganisms, insects, and animals. These can be defensive substances, anti feedants, attractants, and pheromones. Chemotaxonomy is another reason for scientists to study natural products. Chemotaxonomy involves the use of natural products in the classification of species, e.g. alkaloids are typically present in the Annonaceae family especially in Kopsia species, or xanthones are typically present in Garcinia species while coumarins are typical of Calophyllum species. Phytochemical surveys can also reveal natural products that are markers for botanical and evolutionary relationships. The study of natural products have resulted in modern techniques for separation, structural elucidation, screening and combinatorial synthesis have led to increased interest in plant natural products as sources of new drugs. The introduction of herbal products in the form of nutraceuticals and dietary supplements are also changing the plant-based drug market.

INTRODUCTION

Natural products are a renewable source of chemicals and are derived from living things such as plants, microbes and animals. Multidisciplinary approach which consists of botany, ethnobotany, phytochemistry and biological techniques are often involved in the study of natural products. Recently, the use of natural products as nutraceuticals for improving human health has become popular.

Natural product compounds are an important source of medicine. Many countries have well-established systems of traditional medicine. Examples are the Chinese and the Ayurvedic (Geoffrey, 1995). The *Ayurveda* is a record of the plants used in the system of ancient healing in India. Plants used in Egyptian medicine are recorded in the *Ebers papyrus*.

The basis of novel drug discovery has evolved from traditional medicines which are often from plants and given as tea extracts, poultices, powders and other herbal formulations (Samuelsson, 2004). The search for new compounds with biological activities uses the knowledge of ethnobotany and ethnopharmacognosy as a guide. (Sanjay *et al.*, 2007). However, today structure activity-guided organic synthesis, combinatorial chemistry and computational drug design (Schmidt *et al.*, 2008) has overshadowed the role of natural products from plants in drug discovery.

Plant-derived medicinal products has gone a long way in the human pharmacopoeia (Raskin *et al.*, 2004). In 1897, Arthur Eichengrun and Felix Hoffmann made the first synthetic drug, aspirin, while Alexander Fleming discovered penicillin from bacteria in 1928. Two important pharmaceutical drugs derived from botanical sources which have been commercialized include taxol and morphine (Butler, 2004). Arteether is a potent anti-malaria drug recently introduced to the United States market. This drug was derived from artemisinin, a sesquiterpene lactone isolated

from *Artemisia annua* (Graul, 2001; Van Agtmael *et al.*, 1999) and galanthamine, a natural product first isolated from *Galanthus woronowii* Losinsk in Russia (Heinrich *et al.*, 2004; Pirttila *et al.*, 2004). Approximately half of the 250,000 flowering plant species reported in the world are found in the tropical forests most of which can provide chemists with invaluable and potential compounds for development into new drugs. However, only a small percentage of these tropical species have been studied in detail for their pharmaceutical potential (Sanjay *et al.*, 2007). Malaysia, has approximately 12,000 species of flowering plants in her tropical rainforests but only 1,300 of these species have been recorded to be used in traditional medicine (Burkill, 1935).

Cancer is the second leading cause of death in the world. There has been a significant increase in cancer incidence since 1990. Natural product research however, has contributed much to the field of cancer research. (Parkin, 2001). Cancer drugs were 40% natural products or are natural product-derived since before 2002 with another 8% considered natural product mimics (Newman *et al.*, 2003). Some traditionally used medicinal plants have provided medicinally useful known compounds such as indirudin, kamebakaurin, cucurbitacin I, β -lapachone and betulinic acid (Eisenbrand *et al.*, 2004). Known compounds with new biological activities are also important drug leads.

Plant Derived Drugs

Conventional synthetic medicines and drugs can be abusive and can result in addictivity. Incorrect use of these drugs can result in undesirable side effects and many problems. There has been a growing interest recently in alternative therapies and the therapeutic use of natural products, especially those derived from plants (Mentz *et al.*, 1989). A large percentage of the world's population does not have access to conventional pharmacological treatment and folk medicine.

About a quarter of the drugs considered as basic and essential by the World Health Organisation (WHO) originate from plants and a significant number are synthetic drugs derived from natural product precursors. Some examples of important drugs obtained from plants are digoxin from Digitalis spp., quinine and quinidine from Cinchona spp., vincristrine and vinblastine from Catharanthus roseus, atropine from Atropa belladona and morphine and codeine from Papaver somniferum. Sixty percent of anti-tumour and antiinfectious drugs already in the market or under clinical trial are from natural resources origin (Shu, 1998). Syntheses of a majority of these drugs are not economically viable, hence these drugs are still obtained from cultivated or wild plants. Novel or new natural product compounds can be lead compounds for new drugs. They allow for the design of new drugs, synthesis development and the discovery of new therapeutic properties (Hamburger et al., 1991). However, some known compounds obtained from plants such as muscarine, physostigmine, cannabinoids, yohimbine, forskolin, colchicine and phorbol esters are used in pharmacological and biochemical studies (Williamson et al., 1996).

Table 1 shows some plant-based drugs which have been approved/launched during 2000-2006. The novel molecule-based drugs Galanthamine HBr (Reminyl[®]) for the treatment of Alzheimer disease and Miglustat (Zavesca[®]) for Type1 Gaucher disease and Nitisinone (Orfadin) for Antityrosinaemia are in the list among others. See Table 1.

Some plant-derived compounds which have gone through or are presently in clinical trials are shown in Figures 1 and 2.

Year	Generic name	Lead compound	Disease area	Company
2000	Exelon (Rivastigmine tartrate)	Physostigmine	Dementia-Alzheimer's disease	Novartis
	Arteether (Artemotil [®])	Artemisinin	Antimalarial	Brocacef
	Galanthamine HBr (Reminy1 [®]) ^b	Galanthamine	Alzheimer's disease	Shire (U.K.), Johnson & Johnson (U.S.)
	Bexarotene	Retenoic acid derivatives	Cutaneous T cell lymphoma	Ligand Pharmaceuticals
	L-dopa-methyester (Levomet)	L-Dopa	Parkinson's diseases	Chiesi
	Malarone (Atovaquone; proguanil hydrochloride)°	Quinine	Antimalarial	GlaxoWellcome
	Rapacuronium bromide (Raplon)	Tubocurarine	Neuromuscular blocking agent/anaesthesia	Akzo Nobel (Netherlands)
2001	Galanthamine HBr (Reminyl [®]) ^b	Galanthamine	Dementia-Alzheimer's	Janssen Pharmaceuticals
2002	Nitisinone (Orfadin [®])	Leptospermone	Antityrosinaemia	Orphan Pharmaceuticals

	Tiotropium bromide	Tiotropium	Chronic obstructive pulmonary disease	Boehringer Ingelheim
	Avinza (Morphine sulfate)°	Morphine	Pain	Elan
2003	Miglustat $(Zavesca^{\circledast})^d$	1-Deoxynojirimycin	Type1 Gaucher disease	Oxford Glycosides/Actelion/Celltech
2004	Spiriva HandiHaler (Tiotropium bromide) ^c	Tiotropium	Chronic obstructive pulmonary disease	Boehringer Ingelheim
	Apokyn (apomorphine HCl)°	Apomorphine	Parkinson's diseases	Mylan Bertek pharmaceuticals
	Palladone (hydromorphone)		Moderate-to-severe pain	Purdue Pharma L.P.
	DepoDur (morphine sulfate) extended release°	Morphine	Post-surgical pain relief	SkyePharma PLC and Endo Pharmaceuticals
	Belotecan	Campthotecin	Ovarian & small lung cancer	Chong Kun Dang
2005	Tamibarotene (Amnolake)	Retenoic acid derivatives	Acute myelogenous leukaemia	Nippon Shinyaku
	Abraxane (paclitaxel protien-bound particles) ^c	Paclitaxel	Breast cancer	American Pharmaceuticals Partners, Inc./American Bioscience

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	THC:CBD (Sativex) ^e	THC, CBD	MS pain	GW Pharma
2006	Taxotere (docetaxel) injection ^f	Docetaxel	Antineoplastic (head and neck cancer) and stomach cancer	Sanofis-Aventis
	Duodote (atropine and pralidoxine chloride) injection	Atropine	Exposure to organophosphorous nerve agents (Antidote)	Meridian Medical Technologies
	Exelon (rivastigmine tartrate) ^f	Phytostigmine	Dementia-Parkinson's	Novartis
	Hycamtim (topotecan HCl)	Camptothecin	Cervical cancer	GlaxoSmithkline
	Cesamet (nabilone)	Delta-9-THC	Chemotherapy nausea and vomiting	Valeant Pharmaceuticals International
	Polyphenon E (Veregen) Ointment	Green tea polyphenol (catechin) extract	Genital and perianal warts	MediGene AG



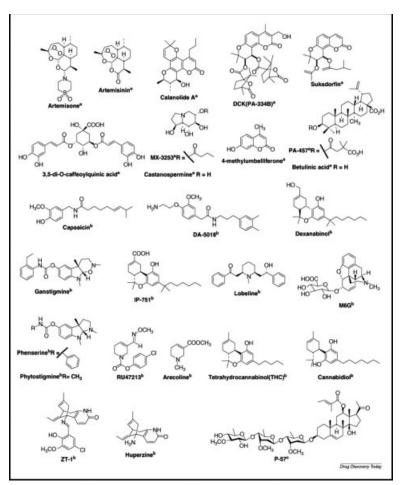
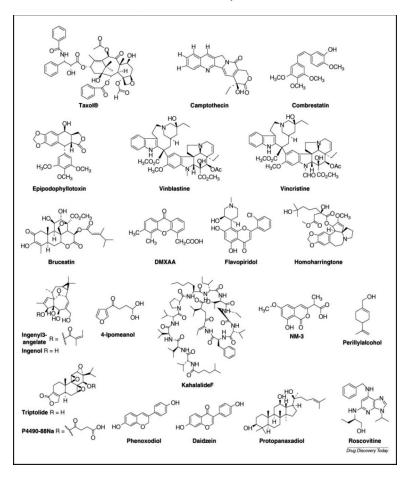


Figure 1 Plant-derived compounds launched/in clinical trials.
(a) Infectious and parasitic disease application, (b) pain and neurological disease application, (c) cardiovascular and metabolic disease application (Arvind et al., 2008).



Natural Products from Malaysian Rainforests

Figure 2 Plant-derived anticancer drugs launched/in clinical trials (Arvind *et al.*, 2008).

Insecticides/pesticides Derived from Plants

Natural product compounds produced by terrestrial plants can defend the plants from herbivores and pathogens. This has led scientists to view higher plants as a valuable source for novel structures that could serve as lead compounds in the development of insecticides/pesticides. Today traditional botanical insecticides play only a minor role in agriculture worldwide even though many plants have been exploited as sources of insecticides/pesticides. Plant natural products which possess insecticidal/pesticidal properties still have potential to encourage and inspire modern agrochemical research. Chemical agents still dominates insecticidal control of disease-transmitting insects such as mosquitoes eventhough development of resistance from longterm use of these chemical insecticides is one main concern. Hence, the search for new natural insecticides from natural resources is an urgent need. Rotenone, pyrethrum and nicotine have been widely used as insect repellants for a very long time. However, with the discovery of synthetic insecticides based on chlorinated hydrocarbons, such as DDT, the use of these compounds was greatly reduced for a period of time. However, these chlorinated compounds induces insect resistance and were proven to be toxic and disastrous for the environment. Thus the use of less toxic compounds based on synthetic or natural pyrethroids is encouraged.

Only a handful of natural products with good insecticidal/ pesticidal activities have been identified from the many hundreds of bioactive compounds tested and isolated. In these tests, feeding deterrence or larval growth inhibition is more common compared to death of the insects. This would probably justify for the handful of botanical insecticides commercialized. Permethrin and fenvalerate, the first two commercial pyrethroids were only discovered in 1973, after the synthesis of allethrin in 1948 and almost 60 years after the structural elucidation of the natural pyrethrins. Azadirachtin from neem seeds is the still the most potent insect antifeedant discovered to date.

Phytochemical Methods

Indigenous use of the plants form the basis of their selection for phytochemical screening. This approach is used in the drug discovery programme. The chemotaxonomic approach or the phylogenetic survey are other plant-collecting methods. Random collection of plant samples is also carried out by researchers especially in areas supporting biological diversity.

Novel drugs have often been provided by natural products isolated from higher plants. Bioassay-guided fractionation and successful purification processes are the key to the success of discovering naturally occurring therapeutic agents. The monitoring of fractions by biological assays to determine the active extracts followed by isolation of active compounds is bioassay-guided fractionation. These compounds are usually responsible for the biological activity of the plant. Bioassay-guided isolation of active compounds requires a strong collaboration between the chemist who carries out the isolation and the biologist who performs the bioassay. In phytochemistry, isolation of compounds is carried out manually by chromatographic techniques such as open column chromatography, flash chromatography, vacuum liquid chromatography and preparative thin layer chromatography. However, automated chromatographic techniques such as high/ medium pressure liquid chromatography and chromatotron plus the availability of pre-packed columns of various polarity allow for successful fractionations and purification of unworkable complex polar mixtures. Separation of complex mixtures have also benefitted from the use of capillary columns in GC together

with GC-MS, which is with equipped with collection of library database. New techniques such as 2D high field NMR, LCMS (liquid chromatography–mass spectrometry), FAB-MS (fast atom bombardment mass spectrometry) and X-ray crystallography also enable natural product chemists to characterize and elucidate structures of small amounts of complicated molecules.

The most active compound will be evaluated against the entire spectrum of molecular targets available in the laboratories to determine whether the compound is specific for the desired target. If the compound is found to interact with the entire family of related targets, its potential side effects or toxicity will be determined.

ANNONACEOUS INSECTICIDAL PLANTS STUDIED

Goniothalamus, Mezzetia and Disepalum Genera

Plants of the genus *Goniothalamus* are usually shrubs or small trees. The leaves are usually coriaceous or membranous; the flowers are usually axillary, sometimes terminal and axillary or cauliflorous. There are a total of 115 species (Sinclair, 1955). These are found in South-eastern Asia and throughout Malaysia. The natives of Malaysia find them useful in traditional medicine in connection with childbirth. They are used in attempts to procure abortion as well as to mitigate the violence of the abortient when they are given after childbirth. The natives of Sarawak find the stem bark of *Goniothalamus andersonii* useful as a natural insect repellent.



Figure 3 The Sepals, Leaves and Trunk of Goniothalamus species



Figure 4 Flowers of Goniothalamuus andersonii and G. Dolichocarpus



Figure 5 Flower of *Goniothalamus malayanus* and fruits of *Goniothalamus umbrosus*

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The *Mezzetia* are usually tall trees. The leaves are leathery with midrib broad and flat above flushed with upper surface and prominent beneath. The flowers are axillary, small, greenish fasciculate or umbellate. The sepals valvate and are small. There are a total seven species.

The genus *Disepalum* are shrubs or small trees found on mountains. The twigs are reddish-brown. The leaves are glabrous, the margins slightly revolute and the midrib sharply angled on the lower surface. The flowers are bisexual, fragrant and yellow tinged with red. The sepals are valvate. The fruits are many, ovoid-oblong and thin-walled. The seeds are 1-2 dark reddish brown and shining (Sinclair, 1955). There are six species available in Peninsular Malaya, Borneo and Sumatra. There are two species available in Peninsular Malaysia.



Figure 6 Flowers and leaves of Mezzetia umbellata

THERAPEUTIC PLANTS FROM THE GUTTIFERAE FAMILY STUDIED

Calophyllum, Mesua, Garcinia and Cratoxylum Genera

This genus has around 180-200 species of tropical evergreen trees in the family Clusiaceae. It is widely distributed in Australasia, Madagascar, Eastern Africa, South and Southeast Asia, the Pacific islands, the West Indies and Latin America (Morel *et al.*, 2000). The common names for *Calophyllum* according to some geographical areas are Bintangor tree in Malaysia, Poon tree in India, and Guanandi, Jacareuba or Santa Maria in Latin America.

Calophyllum plants are wide spread in tropical forests, coastal swamps and coral cays. They are always of large hard wood with shiny and leathery leaves. *Calophyllum* trees grow best in sandy, porous and well-drained soils with direct sunlight. The medium-sized trees can attain 30 m in height and are valued for their hardiness. The bark is usually light grey, while the heartwood is almost brown. On the other hand, the flowers of this tree are always white with a fragrance, and the large round nuts are the main source for seed oil production (Dweck *et al.*, 2002).



Figure 7 The Flower, Fruits and Trunk of Calophyllum inophyllum

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Figure 8 The tree, leaves and fruits of Calophyllum inophyllum

Mesua is a small genus of flowering plants in the family Clusiaceae, native to tropical southern Asia. Common names include ironwood (shared with many other plants) and rose chestnut. *Mesua* trees are evergreen shrubs or small trees which are often buttressed at the base and their height can reach up to 13 m. The trunk is up to 90 cm in diameter at breast height and it is simple, narrow, oblong and dark green. The leaves are whitish on the underside and young leaves are yellowish pink and are arranged in opposite pairs. The blossoms are white and give a nice fragrance.





Figure 9 The tree, new leaves, flowers, old leaves and trunk of *Mesua ferrea*

The *Garcinia* genus comprises 180 species of slow growing trees and shrubs. It is encountered mainly in lowland rainforests of the tropical world (Thoison *et al.*, 2000). Plants from this genus can usually reach 15 to 20 meters in height and have green leaves, edible fruits and yellow latex or resins. In Indonesia, the leaves and seeds of *Garcinia dulcis* have been used for the treatment of lymphatitis, parotitis and struma (Kosela *et al.*, 2000). Meanwhile, traditional healers in the south and central provinces of Cameroon use the bark of *Garcinia lucida* to treat gastric infections and as an antidote against poison (Nyemba *et al.*, 1990).



Figure 10 The Fruits, Leaves and Trunk of Garcinia mangostana

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Figure 11 The tree and leaves of Garcinia nitida



Figure 12 The tree and leaves of Garcinia parvifolia

The wood of *Cratoxylum glaucum* is used by the local communities in Sarawak for house and farm hut construction (Ee *et al.*, 2007). It is a small tree or shrub that can reach 10 m tall, in some rare cases 25 m, and is 45 cm in diameter. The bark is reddish brown and flaky with broadly elliptic, coriaceous leaves. The flowers of *C. glaucum* have crimson petals in a panicle with punctuate glands and small basals. The fruits are 7–10 mm × 3–4 mm in size with persistent sepals of half the capsule length and contains 4–8 seeds per locule.

Natural Products from Malaysian Rainforests

Figure 13 The bark (a), the leaves (b) and the flowers (c) & (d) of *Cratoxylum arborescens*



Figure 14 Flowers and leaves of Cratoxylum glaucum

THERAPEUTIC PLANTS FROM OTHER FAMILIES STUDIED

Artocarpus nitidus, Artocarpus kemando and Artocarpus odoratissimus

Artocarpus is the genus which has the greatest diversity in Indonesia, Malaysia and the Philippines. The genus *Artocarpus* comprises about 60 species distributed from Sri Lanka, India, Pakistan and Indo-China, native to South and South-East Asia, New Guinea and the southern Pacific. 47 species are found in Malaysia. *Artocarpus kemando* and *Artocarpus odoratissimus* are members of the jackfruit family, locally known as *Pudau* and *Terap*, respectively. Both are fairly large evergreen tree.



Figure 15 The Fruits, Leaves and Trunk of Artocarpus species



Figure 16 The Fruits of Artocarpus kemando and leaves of Artocarpus nitidus, trees of Artocarpus nitidus and Artocarpus kemando

Morinda citrifolia

The genus *Morinda* is one of the genera from the Rubiaceae family and it is made up of around 80 species. *Morinda citrifolia* L. is a plant that had been used by the Polynesians for more than 2000 years as food and medicines (McClatchey, 2002; Wang *et al.*, 2002). This small evergreen tree or shrub is native from Southeastern Asia (Indonesia) to Australia and now has a pan tropical distribution. Besides the commercial name, Noni, as used by Hawaiian, the plant is also well-known by its various name called by people over the world: Indian mulberry (Indian subcontinent), mengkudu (Malaysia), nhau (Southeast Asia), painkiller bush (Caribbean)

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or cheese fruit (Australia). The whole plant of Morinda citrifolia has been utilized worldwide for herbal remedies as well as food and dyes. The reddish purple dye from the bark and the yellowish dye from the roots are used to color fabrics and clothing in Java and Hawaii. Besides that, in Java and Thailand, very young leaves are cooked and eaten together with rice. The leaves are also used to make teas to treat malaria (Africa), rheumatism, nausea and arthritis (Philippines). The noni fruits contribute most among the various parts of the plant. They are used to treat lumbago, asthma and dysentery in some regions in Indochina and to treat head lice in Hawaii. The pounded unripe fruits are cooked with salts to be applied to cuts and broken bones. The Malay people drink the juices of over-ripe fruits to regulate the menstrual flow and to ease urinary problems. In certain areas, natives use the fruits for the treatment of toothache, body or intestinal worms, hypertension and mouth and gum infections.



Figure 17 The Fruits, Flower and Leaves of Morinda citrifolia

Ploiarium alternifolium

Emodin which is an anthraquinone was isolated from *Ploiarium alternifolium* (Theaceae). Emodin gave a very low IC_{50} value in the larvicidal bioassay against the larvae of *Aedes aegypti* the vector

of the Dengue Fever virus. This compound is interesting as it can be considered as a potential larvicide against the *Aedes aegypti* mosquito larvae.



Figure 18 Trees and flower of *Ploairium alternifolium*

NEW NATURAL PRODUCTS FROM MALAYSIAN THERAPEUTIC PLANTS

Annonaceae Family

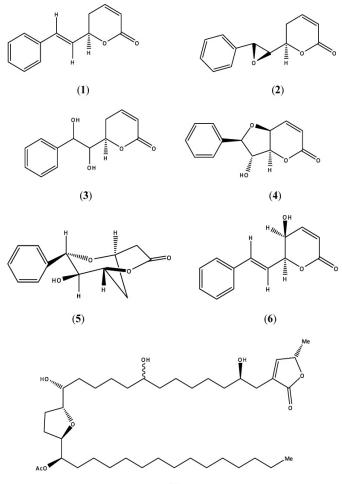
Goniothalamus, Mezzetia and Disepalum genera

Our chemical investigations on the plant species covered larvicidal principles such as annonaceous acetogenins, styrylpyrones, flavonoids, alkaloids and essential oils (mainly sesquiterpenes). Detailed studies were carried out on four *Goniothalamus* species (*G. andersonii*, *G. dolichocarpus*, *G. malayanus* and *G. velutinus*), *Mezzetia umbellata* and *Disepalum anomalum*. The four *Goniothalamus* species provided strylpyrone derivatives (+)-goniothalamin (1), (+)-goniothalamin epoxide (2) (Goh *et al.*, 1995b), (+)-goniodiol (3), (+)-goniothalenol (4), two new natural products (-)-iso-5-deoxygoniopypyrone (5) and

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(+)-5 β -hydroxygoniothalamin (**6**) (Goh *et al.*, 1995a) and essential oils which mainly contained a mixture of sesquiterpenes. The four *Goniothalamus* species also provided very cytotoxic annonaceous acetogenins, the dioxoaporphine ouregidione and goniothalamicin along with the phenanthrene lactam, aristolactam BII and annonacin derivatives. The latter two constituents were also present in *Mezzetia umbellate*. In addition, *G. dolichocarpus* furnished two very cytotoxic flavonoids naringenin and pinocembrin. A new acetogenin, disepalin (**7**) as a waxy semi-solid was isolated from *Disepalum anomalum* (Annonaceae) (Ee *et al.*, 1996).

The crude stem bark extracts of all the plants investigated were screened for their larvicidal activity against the larvae of *Aedes aegypti*. All the crude extracts were mildly cytotoxic. Preliminary *in vitro* cytotoxicity screening against P388 cell lines were carried out on the crude extracts and some bioactivities was detected which collaborates the presence of bioactive acetogenins and some of the styrlpyrone derivatives.



(7)

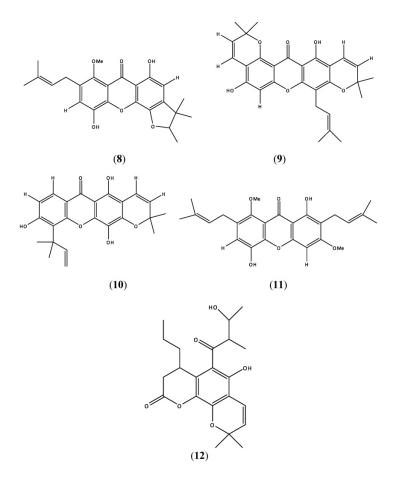
Guttiferae Family

Calophyllum species

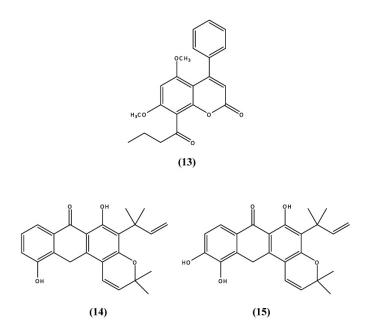
Extensive chromatographic techniques applied to the dichloromethane extract of the stem bark of *Calophyllum inophyllum* resulted in two new xanthones, namely inophinnin (8) (Ee *et al.*, 2011b) and inophinone (9) (Mah *et al.*, 2011a). Meanwhile, the stem bark of *Calophyllum soulattri* afforded two new xanthones, soulattrin (10) (Mah *et al.*, 2011b) and phylattrin (11) (Mah *et al.*, 2012), and a new coumarin, soulamarin (12) (Ee *et al.*, 2011c).

Cytotoxicity screening (MTT Assay) was carried out on all of the crude extracts and pure compounds using nine human cancer cell lines, SNU-1 (stomach), HeLa (cervical), NCI-H23 (lung), Hep G2 (liver), K562 (leukemia), Raji (lymphoma), LS174T (colon), SK-MEL-28 (skin) and IMR-32 (neuroblastoma) cells. The two new xanthones, soulattrin (10) and phylattrin (11), exhibited strong anti-proliferative activity against all of the cell lines with IC₅₀ values less than 10.00 μ g/mL. Another new xanthone, inophinnin (8) are considered as strong cytotoxic agents of the HeLa, SNU-1, NCI-H23, HepG2, K562 and Raji cell lines with IC₅₀ values less than 10.00 μ g/mL. On the other hand, inophinone revealed strong inhibitory activity towards Raji cells and weak inhibitory activity towards other investigated cancer cells. In contrast, soulamarin showed weak cytotoxicity against all the tested cancer cells. Kaempferol and quercetin were used as standard drugs for comparison purposes of all these results.

Antioxidant properties of the new compounds were tested using the DPPH (2,2-diphenyl-1-picrylhydrazyl) radical scavenging method, and ascorbic acid was chosen as the standard agent. The results showed that soulattrin (10) and indicated strong activities with the same IC₅₀ value of 11.72 μ g/mL.



In the past decade, several new xanthones and a new coumarin were successfully isolated from *Calophyllum* species. Mucigerin (13), was obtained from the ethyl acetate extract of *C. mucigerum* (Ee *et al.*, 2004c). In the continuing search for new natural products, the roots of *C. inophyllum* afforded two new xanthones namely inophyllin A (14) (Ee *et al.*, 2006c) and B (15) (Ee *et al.*, 2004b). Inophyllin A (14) induces oxidative stress mediated-apoptosis in Jurkat T lymphoblastic leukemia cells indicated it possesses potential chemo-therapeutic activity (Chan *et al.*, 2012).

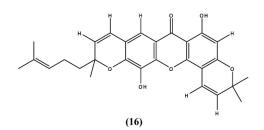


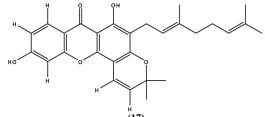
Mesua species

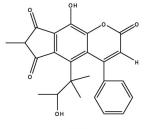
The stem bark of *Mesua beccariana* furnished four new compounds which are two xanthones, mesuarianone (16) and mesuasinone (17) (Teh *et al.*, 2010), a coumarin, beccamarin (18) (Ee *et al.*, 2011d) and a cyclodione, mesuadione (19) (Teh *et al.*, 2012). Meanwhile, three new xanthones were isolated from the root bark of *Mesua ferrea* which are mesuaferrin A (20), mesuaferrin B (21) (Teh *et al.*, 2011) and mesuaferrin C (22) (Ee *et al.*, 2012d). On the other hand, chemical investigations on *Mesua congestiflora* afforded a new benzophenone, congestiflorone (23) (Ee *et al.*, 2012b).

Preliminary screenings were carried out on the new compounds together with the standard drugs, kaempferol and quercetin towards a panel of human cancer cell lines. The human cancer cell lines tested were Raji, SNU-1, K562, LS-174T, SK-MEL-28, IMR-32, HeLa, Hep G2 and NCI-H23. Several compounds exhibited dosedependent inhibition of proliferation against all the cell lines. The cytotoxicity of mesuaferrin A (20) was strong as it possesses significant inhibitory effects against all the tested cell lines. Furthermore, mesuaferrin B (21) demonstrated strong cytotoxic activity against nearly all the tested cancer cell lines except for IMR 32 and Raji cells which it exhibited mild activity only. Mesuasinone (17), beccamarin (18), mesuadione (19) and congestiflorone (23) gave strong inhibitory activity towards Raji cells. Besides that, three new compounds mesuarianone (16), mesuasinoine (17) and mesuadione (19) indicated strong cytotoxicity against K562 cells. The cervical cells HeLa was strongly inhibited by mesuasinone (17) and beccamarin (18). The remaining compounds revealed mild to weak cytotoxicity activities against all the investigated cancer cells. Preliminary insights towards the structure-activity relationships among a series of xanthone derivatives were studied. The substituent groups comprising diprenyls, dipyranos and prenyl pyrano of the xanthone derivatives promise cytotoxicity towards almost all the tested cancer cell lines (Teh et al., 2013).

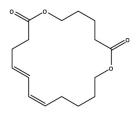
Only mesuaferrin A (20) revealed mild scavenging potential against the DPPH radical with EC_{50} values of 11.72 µg/mL. The rest of the new compounds possess no free radical scavenging activity.



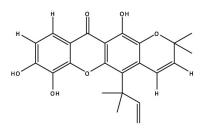






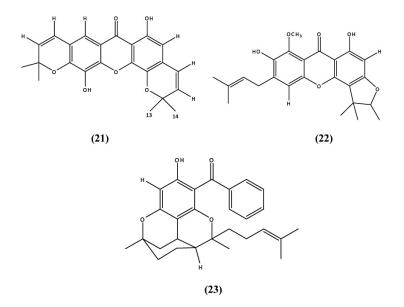


(19)

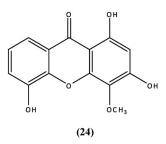


(20)

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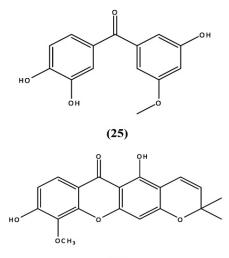


An earlier study on the chemical constituents from the stem bark of *Mesua daphnifolia* furnished a new tetraoxygenated xanthone, daphnifolin (**24**) (Ee *et al.*, 2006d). This compound was tested *in vitro* for its cytotoxic activities against four cancer cell lines, which are MDA-MB-231 (Human estrogen receptor negative breast), HeLa, CEM-SS (T-lymphoblastic leukemia) and CaOV3 (Human ovarian cancer). However, it gave weak anti-proliferation effects against all the investigated cells (Ee *et al.*, 2005b).



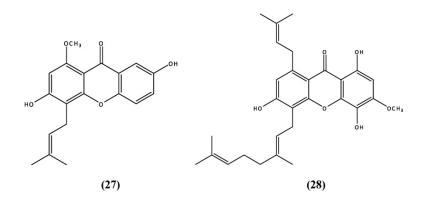
Garcinia species

Our recent phytochemical investigation on the *Garcinia eugenifolia* roots and *Garcinia nitida* stem bark gave a new benzophenone, (3,4-dihydroxyphenyl)(3-hydroxy-5-methoxyphenyl) methanone (**25**) (Jong *et al.*, 2012) and a new xanthone, 1,6-dihydroxy-5-methoxy-6,6-dimethylpyrano[2',3':2,3]-xanthone (**26**) (Ee *et al.*, 2012a), respectively.



(26)

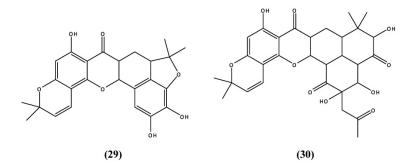
A chemical survey on *Garcinia mangostana* stem (Ee *et al.*, 2006a) and *Garcinia cuneifolia* stem bark (Ee *et al.*, 2003) were embarked for their chemical constituents. Two new xanthones, mangosharin (27) and cuneifolin (28) were successfully isolated from these plants, respectively. All the crude extracts together with the new compound were assayed against the larvae of *A. aegypti*. The ethyl acetate extract of *G. mangostana* indicated strong toxicity with an LC₅₀ value of 30.1 μ g/mL, while other extracts from both species showed moderatel toxicity towards the larvae. On the other hand, the hexane extract of the former plant gave strong cytotoxicity against CEM-SS cell line with IC₅₀ value of 17.0 μ g/mL. However, mangosharin showed no activity against the larvae (Ee *et al.*, 2006a) and weak cytotoxicity against CEM-SS cells (Ee *et al.*, 2008).

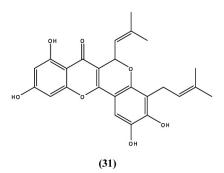


Moraceae Plants

Artocarpus species

Chemical investigations of the stem bark of *Artocarpus kemando* and *Artocarpus odoratissimus* (Moraceae) have resulted in the isolation of three new constituents. Two new flavonoids, artomandin (**29**) and kemandonin (**30**) were isolated from the acetone extract of *A. kemando* whereas another new flavonoid, artosimmin (**31**) was obtained from the ethyl acetate extract of *A. odoratissimus*. A cytotoxic study showed that artomandin and artosimmin were significantly active against the HL-60 (Human promyelocytic leukemia) and MCF-7 (Human breast adenocarcinoma) cell lines with IC₅₀ values less than 3.5 μ g/mL. Moreover, kemandonin exhibited significant growth inhibition towards HL-60 and moderate cytotoxicity towards MCF-7 with IC₅₀ values of 6.9 and 13.1 μ g/mL, respectively. Besides, artomandin and artosimmin gave moderate scavenging effect towards the DPPH radical test with EC₅₀ values of 38.0 and 32.1 μ g/mL as well (Ee *et al.*, 2010d; Ee *et al.*, 2011e).

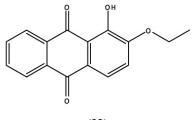




Rubiaceae Plants

Morinda species

An investigation of *Morinda citrifolia* (Rubiaceae) roots afforded a new anthraquinone, 2-ethoxy-1-hydroxyanthraquinone (**32**) (Ee *et al.*, 2009b). The structure of the compound was elucidated based on NMR, IR and MS. Biological evaluation of all the crude extracts against the larvae of *Aedes aegypti* indicated the chloroform extract to exhibit promising larvicidal activities with LC_{50} value of 1.8 µg/ mL (Wen *et al.*, 2009).



(32)

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BIOGRAPHY

Professor Dr Gwendoline Ee Cheng Lian was born in Kuching, Sarawak. She received both her early and secondary education at St. Teresa's Primary and Secondary School and her HSC education at St. Thomas' Secondary School in Kuching. She later obtained her BSc degree in Chemistry from Waikato University in New Zealand and her MSc degree in Organic Chemistry from the same university. She received her PhD degree in Natural Product Chemistry from University of Malaya, Malaysia.

Professor Gwendoline Ee began her career as a lecturer in Universiti Pertanian Malaysia Sarawak campus in 1981. She later transferred to UPM Serdang campus in 1996. She is active in her research in the field of Natural Product Chemistry and has authored and coauthored about 130 journal manuscripts in international refereed journals and local journals as well and about 110 articles in conferences and seminars. Her teaching duties comprise teaching students at both undergraduate and postgraduate levels. The courses taught are mainly on spectroscopy, organic chemistry and natural product chemistry. She has supervised and cosupervised many postgraduate students at Masters and Phd levels as well as undergraduate students carrying out final year projects in natural product Chemistry.

Prof Gwendoline Ee was also actively involved in organising seminars and conferences at international and national levels. She is also a member of IKM, RSC, MNPS and ACS. She also serves as a reviewer of journal articles to a number of international and national journals. She is also involved in assessing research grant applications at both faculty and university levels.

She has received excellent service awards at university level in 2001 and 2006 and also certificates for being an excellent lecturer as well as certificates for excellent researcher every year from 2002

until 2012 at faculty level. She was also awarded with the "Adi pengajar" award at faculty level in 2008.

As a researcher, Professor Gwendoline Ee has headed four (4) EA IRPA projects, four (4) short term research projects, two (2) Science Fund projects, two (2) FRGS projects and three (3) RUGS projects. These research projects have resulted in numerous journal publications in international journals.

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