Syarahan Inaugural

PROF. DR. MAWARDI RAHMANI

Bertajuk

CHEMICAL DIVERSITY OF MALAYSIAN FLORA: Potential Source of Rich Therapeutic Chemicals

- 26 Julai 2003
- Dewan Taklimat Tingkat 1,
  Bangunan Pentadbiran Universiti Putra Malaysia

UNIVERSITI PUTRA MALAYSIA

CHEMICAL DIVERSITY OF MALAYSIAN FLORA: POTENTIAL SOURCE OF RICH THERAPEUTIC CHEMICALS

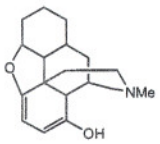
ABSTRACT

Although people all over the world has been using various kind of plant species as medicine for the treatment of diseases since millennia, the isolation and identification of the active principals were only achieved in the 19th century. This can be considered the beginning of remarkable achievements in the discovery of therapeutic agents from plants. Some of these early discoveries are the isolation of morphine from *Papaver somniferum*, aneasthetic cocaine from *Erythroxylum coca*, antimalarial quinine from *Cinchona officinalis* etc. Numerous other therapeutic molecules have been discovered since and the general health of the world population improved dramatically, the search for new drugs from plants, microorganisms and marine source continued until today. With the availability of modern techniques, instrumentations and advancement in scientific knowledge have led to faster phase of discovery of therapeutic chemicals with wide ranged of structural types. It has been estimated that less than 1% of plant species has been examined in detailed for their therapeutic potential and currently about 120 pharmaceutical products in used are derived from plants and 75% of these were discovered from plants used in traditional medicine. In this presentation we will look into the diversity of chemicals isolated and fully characterized from our own rich Malaysian tropical flora. Amongst the various type of natural products identified are the many classes of alkaloids, lignans, terpenoids, sulphur-containing compounds, flavonoids, xanthones, glycosides, chalcones etc. Particular attention was made on certain genus of plants from the Rutaceae family (lemon family) due to the presence of interesting chemical structures and exhibiting good biological activity. From the various types of compounds identified, certain classes of alkaloids, coumarins and sulphur-containing compounds have shown excellent antimicrobial and anticancer activity against various cancer cell lines. With the availability of high-throughput screening tests for bioassay-guided fractionation and combinatorial synthesis tool, natural product from plant source particularly from tropical plants, will continue to supply banks of compounds for future drug developments

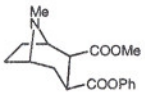
INTRODUCTION

It has been recognized amongst natural product chemists and phytochemists that plant species contain vast array of secondary metabolites. One of the most compelling explanations for the chemical diversity within the biological system in the tropical plants is the science of chemical ecology. Plants living in tropical environment have to develop and survive under continuous and intense competition for nutrients and resources. At the same time, the plants also have to develop an array of chemical defenses to protect them from viral diseases, fungal pathogens, insects and other predators. Thus, tropical plants are perhaps the most valuable source of new bioactive chemical entities due to their biodiversity coupled with the chemical diversity found within each species. A large number of species has been superficially examined for their pharmacological and medicinal application, but it is estimated the less than 1% has been thoroughly examined for their potential use as novel therapeutic agents. Over 120 pharmaceutical products currently in use are plant derived and 75% of these were discovered by from plants use in traditional medicine [1]. Table 1 illustrates some of the priceless and important therapeutic chemicals, mostly alkaloids, isolated and structurally identified.

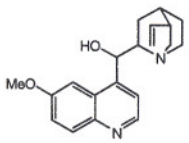
In most part of the world people has been using various kind of plant species as medicine for millennia. In fact Chinese and Indian great civilizations have provided written documents in utilizing plant species for the treatment of various ailments by their people. The isolation and identification of the active principals from these medicinal plants were only achieved in the 19th century and this was the beginning of remarkable achievement in the discovery of therapeutic agents from plant source. Some of the remarkable discoveries are the isolation of morphine by French pharmacists Peletier and Caventou in 1812 from *Papaver somniferum* for the relieve of unbearable pains; the aneasthetic cocaine from *Erythroxylum coca* in 1860; the antimalarial quinine from *Cinchona officinalis*; the parasympatholytic atropine from *Atropa belladonna*; and more recently the anticancer vinblastine and vincristine from *Catharanthus roseus*. Other examples of therapeutic molecules are ephedrine, colchinine and reserpine. Although numerous useful therapeutic molecules have since been discovered and the general health of the world population improved drastically, there is still a serious need of drugs for the treatment of cancer, infections and new diseases.



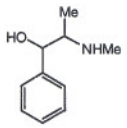
Morphine



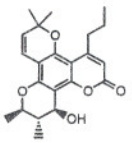
Cocaine



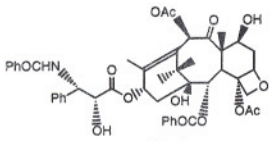
Quinine



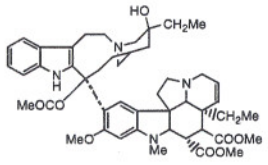
Ephedrine



(+)-Calanolide A



Taxol

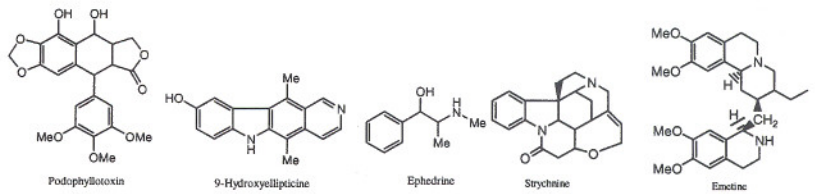


Vinblastine

PLANT DERIVED DRUGS AND THEIR POTENTIAL

In view of discovering new drugs, intensive survey of plants, microorganisms and marine animals for antitumour activity began in the late fifties and over the last 40 years a vast number of plant extracts were tested for antitumour activity. About four percent of this extract have shown reproducible activity and the antitumour-inhibitory principles isolated in the screening tests were usually new natural products spanning a wide range of structural types [2, 3]. However, therapeutic agents for the treatment of various diseases are synonym with heavy side effects and unacceptable mortality rates such as in the case of cancer treatment. For example, fungal infections and AIDS were treated with a few costly drugs such as amphotericin which induced heavy side effects. Thus, it appears that research on natural products for their therapeutic potentials remains of fundamental importance.

Recently the most promising plant-derived anticancer agents found during these screening tests were taxol and 9-hydroxyellipticine. Taxol is a diterpene isolated from Pacific Yew tree, *Taxus brefivolia*, which has demonstrated encouraging responses in clinical trials in ovarian and breast cancer and is now the first drug of choice in several tumorous cancer [4]. Quatemization of 9-hydroxyellipticine isolated from *Ochrosia elliptica* lead to the formation of 9-hydroxyellipticine acetate, a compound of great potential in the treatment of some forms breast cancer [5]. Both vincristine and vinblastine, discovered in the 1950s from periwinkle *Catharanthus roseus*, were also drugs of choice in many forms of leukemia and it has increased the survival rate of childhood leukemias by 80%. Many other cytotoxic principles were also identified recently such as podophyllotoxin and etoposide from Podophyllum peltatum, betulinic acid from *Betula alba*, ephedrine from *Ephedra sinica*, strychnine from *Strychnos nux-vomica*, elephantopine from *Elephantapus elatus* and a range of steroidal cucurbitacins from Cucurbitaceae family [6].



Many other plant-derived drugs have also received approval for production for the treatment of various kinds of cancers. Topocetan, an analog (a synthesized form) of an alkaloid discovered in *Camptotheca acuminata*, has been used either alone or in combination with other anticancer drugs for the treatment of ovarian and small cell lung cancers. Another analog discovered from the same plant, irinocetan, has also been used in the treatment of metastatic colorectal cancer. Some cytotoxic principles as shown in vitro assays were drop from being further investigated due to heavy side effects in clinical trials. Emetine isolated from *Cephaelis ipecacuanha* and nitidine from *Zanthoxylum nitidum* exhibited exceptional antileukaemic activities but were dropped due erratic toxicity [7]. Similarly, camptothecine, a pyrroloisoquinoline alkaloid isolated from *Camptotheca acuminata* showed broad-spectrum of activity and performed a fair response in limited clinical trials, but due to high toxicity and poor solubility, the investigation was discontinued [8].

Virus diseases remain an area of medicine for which specific treatments are lacking and added impetus was given in the search of antiviral drugs by recognizing that the retrovirus termed human immunodefiency virus (HIV) was the causative agent of AIDS. Considerable financial investments were initiated by pharmaceutical companies and various government agencies in developed countries for large scale screening program of natural products from plant source and synthetic compounds. Since then some positive results have been obtained on natural products with anti-HIV property. One such an important discovery is the isolation and characterization of calanolide A, a dipyranocoumarins, from *Calophyllum lenigerum* var. *austrocoriaceum* and calanolide B from *Calophyllum teysmanii* var. *inophylloides*, trees found in Sarawak. Both compounds are representatives of distinct class of non-nucleoside HIV-1 specific reverse transcriptase inhibitor under development as an AIDS chemotherapeutic agent (Kashman et al., 1992 and Boyd et al., 1997) [9, 10]. Calanolide A is currently is early clinical trials in the United States.

The development of robotics for high-throughput random screening in the early 1990's with the ability to handle large number of sample with the aim of obtaining new bioactive compounds, has rekindled interest in examining tropical plant species. This has triggered other activities in natural product chemistry, pharmacognosy and ethnomedical research. The search for new natural products is widely recognized as an interdisciplinary process with the involvement of many steps such as the following. Ideally all the steps should be carried out in order to establish the true potential of particular compounds or plants. However, due to limited resources and constraint some of these steps were skipped.

1. collection, scientific identification and preservation of the biological samples
2. preparation of appropriate extracts and preliminary chromatographic analysis
3. biological and pharmacological screening of crude extracts
4. consecutive steps of chromatographic separation, with bioassays for each fractions
5. verification of the purity of the isolated compounds
6. structural elucidation by spectroscopic/chemical method
7. partial or total synthesis
8. preparation of derivatives/analogues and structure-activity relationship
9. large-scale isolation for further pharmacological and toxicological tests

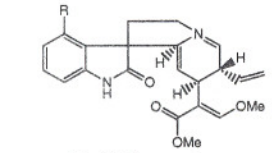
Table 1. Plant-based therapeutic chemicals

No.	Drug/Chemical	Action/Clinical use	Plant source
1.	Acetyldigoxin	Cardiotonic	*Digitalis lantana*
2.	Ajmalicine	Circulatory disorders	*Rauvolfia sepentina*
3.	Anabesine	Skeletal muscle relaxant	*Anabasis sphylla*
4.	Asiaticoside	Vulnerary	*Centella asiatica*
5.	Atropine	Anticholinergic	*Atropa belladonna*
6.	Berberine	Baccillary dysentery	*Berberis vulgaris*
7.	Betulinic acid	Anticancerous	*Betula alba*
8.	Caffeine	CNS stimulant	*Camellia sinensis*
9.	Camptothecin, irinotecan	Anticancerous	*Camptotheca acuminata*
10.	(+)-Catechin	Haemostatic	*Potentilla fragarioides*
11.	Cocaine	Local anaesthetic	*Erythroxylum coca*
12.	Codeine	Analgesic, antitussive	*Papaver somniferum*
13.	Colchinine	Antitumor, anti-gout agent	*Colchicum autumnale*
14.	Curcumin	Choleretic	*Curcuma longa*
15.	Danthron	Laxative	*Cassia species*
16.	Digitalin, digitoxin, digoxin,	Cardiotonic	*Digitalis purpurea*
17.	Ephedrine	Antihistamine	*Ephedra sinica*
18.	Etoposide	Antitumor agent	*Podophyllum peltatum*
19.	Glycyrrhizin	Sweetener	*Glyrrhiza glabra*
20.	9-Hydroxyellipticine	Anticancer	*Ochrosia elliptica*
21.	Menthol	Rubefacient	*Mentha species*
22.	Methyl salicylate	Rubefacient	*Gaultheria procumbens*
23.	Morphine	Analgesic	*Papaver somniferum*
24.	Nicotine	Insecticide	*Nicotiana tabacum*
25.	Papain	Proteolytic, mucolytic	*Carica papaya*
26.	Papavarine	Smooth muscle relaxant	*Papaver somniferum*
27.	Podophyllotoxin	Antitumor, anticancer	*Podophyllum peltatum*
29.	Quinine, quinidine	Antiarrhythmic, antimalarial	*Cinchona ledgeriana*
30.	Reserpine, rescinnamine	Antihypertensive	*Rauvolfia serpentina*

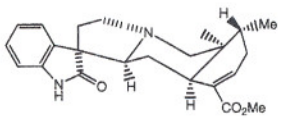
No.	Drug/Chemical	Action/Clinical use	Plant source
31.	Rotenone	Piscicide, insecticide	*Derris elliptica, Lonchocarpus*
32.	Scopolamine	Sedative	*Datura species*
33.	Sennosides A, B	Laxative	*Cassia species*
34.	Stevioside	Sweetener	*Stevia rebaudiana*
35.	Strychnine	CNS stimulant	*Strychnos nux-vomica*
36.	Taxol	Antitumor agent	*Taxus brevifolia*
37.	Teniposide	Antitumor agent	*Podophyllum peltatum*
38.	Topocetan	Anticancer	*Camptotheca acuminata*
39.	Tubocurarine	Abortifacient	*Clorodendron tomentosum*
40.	Vasicine	Cerebral stimulant	*Vinca minor*
41.	Vinblastine, vincristine	Antiluekemic agent	*Catharanthus roseous*
42.	Yohimbine	Aphrodisiac	*Pausinylstalia yohimbe*

THE DIVERSITY OF NATURALLY OCCURRING COMPOUNDS FROM TROPICAL PLANTS

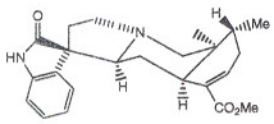
One of the most important starting points in carrying out natural product work is the systematic phytochemical survey of our rich tropical plants for the presence of alkaloids, terpenes and saponins together with their biological activities. A number of these surveys were conducted not only in the Peninsula Malaysia, but also in Sabah and Sarawak. In one of these works, 216 plant species representing 150 genera and 50 families were collected and screened for the three classes of compounds. 28 species (13%) gave s positive test for alkaloids, 86 species (40%) for saponins and 55 species (25%) for triterpenes/steroids [11]. Two of the alkaloid containing plants were collected in bulk for further detailed phytochemical works in the laboratory, the *Uncaria cordata* and *Uncaria borneensis*, both are medium size creepers with curve hook for climbing of the Rubiaceae family. Genus *Uncaria* is one of the species that has received much attention amongst researchers since a large number of the species are reported to be of medicinal values, including the widely investigated *Uncaria gambir*, From *Uncaria cordata*, two major indole alkaloids corynoxeine and corynoxine B and a number of minor constituents were isolated and identified. From the related species, *Uncaria borneensis*, three indoles isomers were isolated and identified as uncarine E, unicarine D and uncarine C [12].



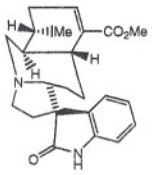
R = H, Corynoxeine
R = OMe, Corynoxine B



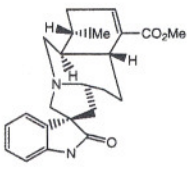
Uncarine C



Uncarine D



Uncarine E



Uncarine F

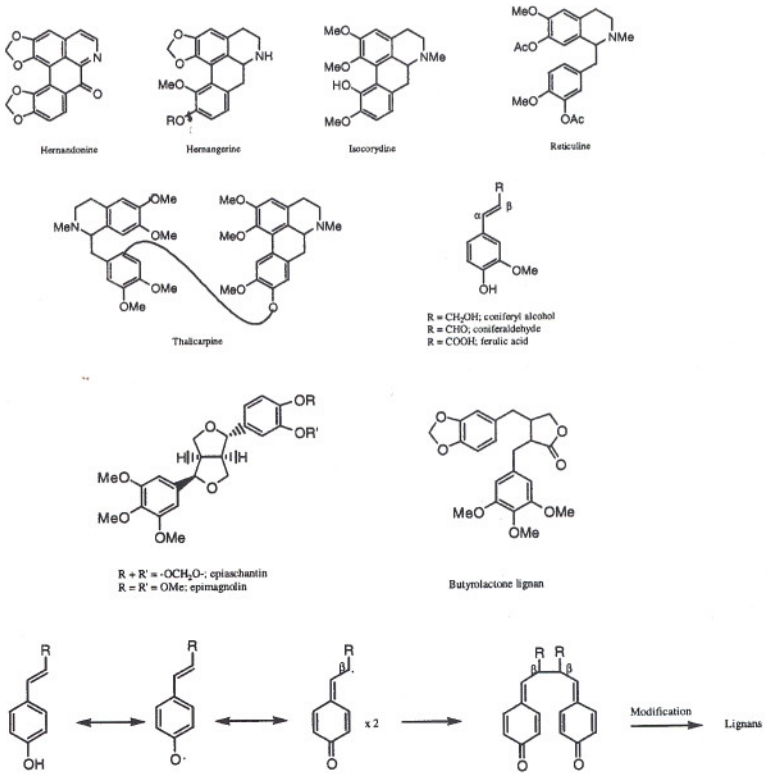
Each of these stereoisomers could be converted to the other by refluxing them in either aqueous acetic acid or pyridine solution to give mixtures of the three isomers with the appearance of a new fourth isomer identified as uncarine F (6) as given in Table 2. The ready formation of the equilibrium mixture from each of the stereoisomers is most likely a result of epimerisation at both C-3 and C-7 centres and a plausible reaction mechanism is as given below:

Table 2. Equilibrium reaction results of the isomers

	Reflux with aqueous acetic acid (4 hours)			
Compounds	Products (%)			
	Isomer C	Isomer D	Isomer E	Isomer F
Isomer C	45	40	10	5
Isomer D	45	40	10	5
Isomer E	45	40	10	5
	Reflux with pyridine solution			
Isomer C	70	5	20	5
Isomer D	40	0	40	20
Isomer E	5	5	85	5

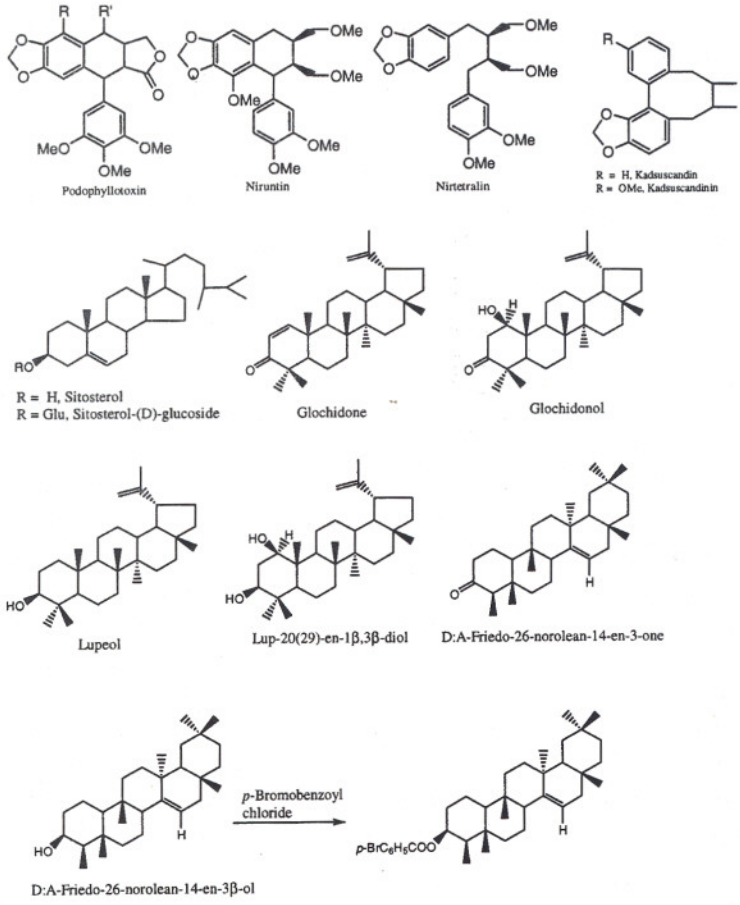
Another alkaloid rich containing plant investigated was *H. nymphaefolia* with the identification of three aporphine hernandonine, hernangerine and isocorydine; one benzylisoquinoline reticuline and one benzylisoquinoline-aporphine dimmer, thalicarpine [13]. This medicinal plant is widely used especially in Fiji Islands for the treatment of

urinary infection, menstrual pain and early recovery after giving birth. The plant is also rich in lignans, the dimers of phenylpropanoids as exemplified by compounds such as eugenol, coniferyl alcohol, coniferaldehyde and ferulic acid. These lignans are derived through the β, β-coupling of the side chains of two penylpropanoid units followed by structural modifications. The three lignans isolated and identified are the epiaschantin as the major component, epimagnolin and butyrolactone lignan. The stereochemical and absolute configuration of the epiaschantin was resolved by preparing a bromo derivative and single crystal X-ray analysis [14, 15]. The neutral fraction of another related species, *Hernandia peltata*, also gave the same three lignans but with different percentage composition.



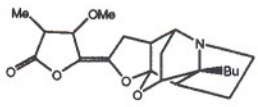
Some lignans are well known to have strong biological activity such as podophyllotoxin which is currently being used as commercial drug for anticancer treatment originally isolated from the resin of *Podophyllum* species [6]. Other lignan-cotaining plants investigated in our laboratory are the extracts of leaves of *Phyllanthus niruri* (dukung anak) and *Kadsura scanden* with the identification of lignans niruntin, nirtetralin, kadsuscandin and kadsuscandinin [16]. Phyllanthus species contain plants of useful medicinal application and several biologically important constituents, including anticancer agents, have been

isolated from members of this genus. We have also investigated the constituents of a related species, *Phyllanthus watsonii*, an endemic plant collected from Endau Rompin Forest Reserve. From this two new unsaturated nor-triterpenes, 26-nor-D:A-friedoolean-14-en-3-one and 26-nor-D:A-friedolean-14-en-3β-ol together with lupenyl palmitate, friedelin, epi-friedelanol, glochidone, glochidonol, lup-20(29)-en-1β,3β-diol, sitosterol and sitosterol-β-(D)-glucoside were isolated. The structures of the new compounds were established by detailed spectral analyses, chemical conversion of 26-nor-D:A-friedoolean-14-en-3-one to 26-nor-D:A-friedolean-14-en-3β-ol by oxidation with CrO_3 in pyridine and single crystal X-ray analyses of *p*-bromobenzoyl derivative of the later [17, 18].

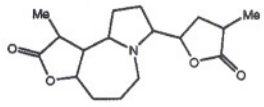


While carrying phytochemical survey work in Ipoh we came across a small creeper giving exceptionally strong alkaloid test results. This creeper was identified as *Stemona tuberosa*, locally called as 'ubi kemili hutan, which bears large quantity of long and slender tubers

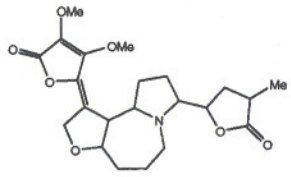
and used in traditional preparation to cure backaches and sold at night market and roadside peddlers. Extraction of the tubers resulted in the isolation of alkaloids stemofoline, stemonine and protostemonine [19, 20].



Stemofoline



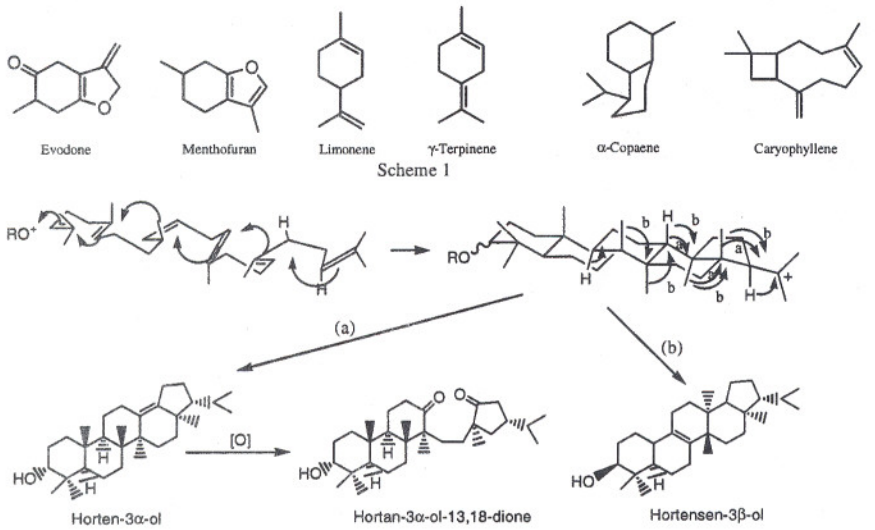
Stemonine



Protostemonine

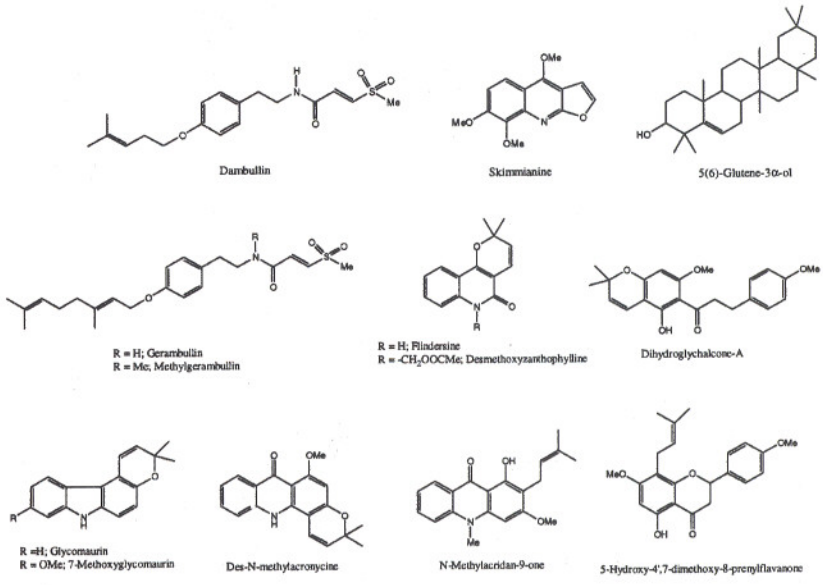
RUTACEOUS PLANTS AS SOURCE OF INTERESTING COMPOUNDS

One of the plant families we had investigated in detailed for the last coupled of years is on Rutaceae, lemon family, due to its interesting and wide spectrum of structural-types. Members of the family are widely used in traditional medicine and exhibited excellent biological activity. Some of the genus we have investigated were the *Glycosmis*, *Micromelum*, *Murraya*, *Melicope* and *Acronychia* species. One of our earlier works on the Rutaceae family was on the volatile and non-volatile components of *Euodia hortensis* (*Melicope hortensis*). Currently this genus has been revised and placed under *Melicope*. The main features of the leaf oil are the occurrence of a large amount of menthofuran (64%) and significant quantities of evodone (17%), γ-terpinene (6%), perillyl acetate (6%) and limonene (5%). The percentage composition of evodone (44%) in the flower oil is substantially larger with corresponding decrease in the amount of menthofuran (7%). Other substantial components of the flower oil are the α-copaene (8%), caryophyllene (5%) and ar-curcumene (15%) [21]. Menthofuran is a commercially important compound in the perfumery industry and it is currently obtained from peppermint, *Mentha piperita* and *M. silvestries*. The occurrence of large quantity of menthofuran in *M. hortensis* suggest that this plant may be of potential commercial importance as a source of this compound. Other non-volatile components isolated and identified from the plant are the triterpernes horten-3α-ol, hortensen-3β-ol and hortan-3α-ol-13,18-dione. The structure assignments were confirmed by a single crystal X-ray analysis and conversion of horten-3α-ol to hortan-3α-ol-13,18-dione by oxidative cleavage of the double bond [22]. A possible biogenesis for the formation of these compounds has also been proposed as shown in Scheme 1.

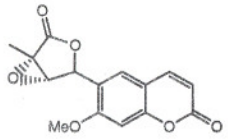


From the six *Glycosmis* species we have investigated many classes of compounds were identified including alkaloids, coumarins, flavones, sulphones, triterpenes etc. Some extracts and pure compounds of *Glycosmis* species were found to be strongly active when tested against various bioassay systems. The compounds responsible for giving this activity were monitored by TLC plates and spraying the plates with spore suspension of indicator fungus prepared from *Aspergillus flavus*. From *Glycosmis calcicola*, the major contributors to this activity were due to the presence of flindersine and desmethoxyzanthophiline [23, 24].

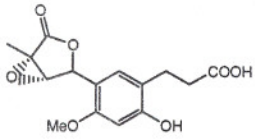
Glycosmis species is one of the very few plant species known to contain sulphur-containing compounds [25, 26]. One of the interesting sulphur-containing compounds we have isolated and identified is methylgerambullin, a sulphone obtained from the same plant. The compound exhibited only mild antifungal activity but gave excellent results when tested on a series of cancer cell lines. The IC_{50} values obtained were 0.25, 1.2, 1.5 and 1.7 μg/ml against CEM-SS, KU812F, HT29 and UACC cell lines, respectively. When tested on CEM-SS cell line, the concentration used is comparable to standard drug. Time-course study revealed that the compound killed cells directly by causing cell necrosis but do not exhibit cell proliferation of the unaffected cells. Complete cell disintegration and severe cell rupture were observed microscopically and this phenomenom became more extensive with prolong exposure [27]. Other members of the genus investigated were the *G. chlorosperma*, *G. mucronantha*, *G. latifolia*, *G. cochchichinensis* and *G. citrifolia* with the identification of compounds such as dambullin, gerambullin, 5(6)-glutene-3α-ol, N-methylacridan-3-one, glycomaurin, des-N-methylacronycine, skimmianine, dihydroglychalcone-A, 5-hydroxy-4',7-dimethoxy-8-prenylflavanone etc [24]. The $CHCl_3$ extracts of both *G. chlorosperma* and *G. cochchichinensis* exhibited strong activity against T-lymphoblastic cell line (CEM-SS) with IC_{50} values of 1.5 and 0.75 μg/ml. Study on this is still being pursuit but we suspect this activity is due to the presence of another sulphur-containing compounds, dambullin and gerambullin, isolated from these plants.



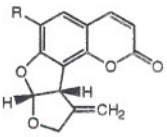
Only two species of *Micromelum* occurred in Malaysia, *Micromelum minutum* and *M. hirsutum*. However, only *Micromelum minutum* has been collected in three separate locations with the isolation and identification of interesting coumarins and triterpenes. A sample collected in Pahang gave the typical coumarin, micromelin and a novel dihydrocinnamic acid derivative which was identified as 1,2-seco-dihydromicromelin. The second sample collected from Kelantan, gave two new tetracyclic coumarins microminutinin and 6-methoxymicrominutinin which possess a fused bifurano system that appears to be derived by cyclization of a 7-oxygenated-8-(1,2-dimethoxy)propylcoumarin precursor. These compounds may be substituted at C-6 (as in micromelin) or at C-8 (as in microminutinin) with prenyl side-chain based on either the normal 3,3-dimethylallyl unit or the unusual 1,2-dimethylpropyl init [28-30]. A group of new class of coumarins were also isolated from the third collection of Micromelum minutum from Sabah and identified as 3",4"-dihydrocapnolactone, 2',3'-epoxyisocapnolactone, 8-hydroxyisocapnolactone-2',3'-diol, 8-hydroxy-3",4"-dihydrocapnolactone-2',3'-diol and 8,4"-dihydroxy-3",4"-dihydrocapnolactone-2',3'-diol. Triterpenes such as 5(6)-gluten-3-one and 5(6)-gluten-3α-ol were also isolated from this collection [31]. The major component 2',3'-epoxyisocapnolactone and 8-hydroxyisocapnolactone-2',3'-diol were significantly toxic to CEM-SS and HL60 cell lines. The IC_{50} values of the former against these two cancer cell lines were 3.9 and 4.2 µg/ml, while those of the latter were 2.9 and 2.5 µg/ml, respectively. Further detail bioassay works on these compounds are still being pursued. This study confirmed the occurrence of distinctive chemical varieties in *Micromelum minutum*.



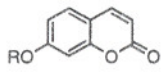
Micromelin

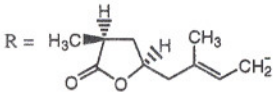


1,2-seco-dihydromicromelin

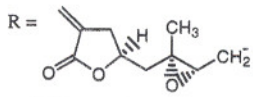


R = H, Microminutini
R = OMe, 6-Hydroxymicrominutinin

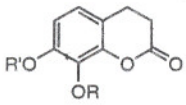


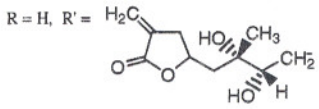


3",4"-Dihydrocapnolactone

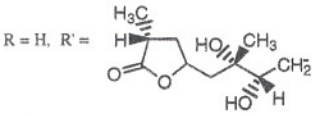


2',3'-epoxyisocapnolactone

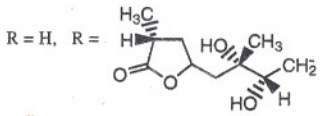




8-Hydroxyisocapnolactone-2',3'-diol

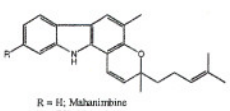


8-Hydroxy-3",4"-dihydrocapnolactone-2',3'-diol

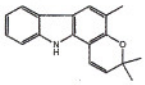


8,4"-dihydroxy-3",4"-dihydrocapnolactone

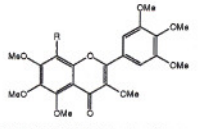
Other medicinal plants from Rutaceae family being investigated in detail are the *Murraya* and *Zanthoxylum* species with the isolation and identification of alkaloids, flavonoids, coumarins, glycosides and terpenoids depending on the location of plant collected. Some of the compounds identified from *Murraya koengii* (daun kari) and *Murraya paniculata* (kemuning) were mahanimbine, girinimbine, murrayanine, mahanine, 3,5,6,7,3',4',5'-heptamethoxyflavone, 3,5,6,7,8,3',4',5'-octamethoxyflavone etc. Some of these compounds were mildly active when tested against six pathogenic fungi and bacteria [32-36].



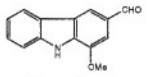
R = H; Mahanimbine
R = OH; Mahanine



Girinimbine



R = H; 3,5,6,7,3',4',5'-Heptamethoxyflavone
R = OMe; 3,5,6,7,8,3',4',5'-Octamethoxyflavone

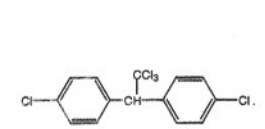


Murrayanine

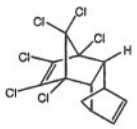
SEARCH FOR NEW INSECTICIDES FROM PLANTS

It was believed at first that DDT is universal insecticides which can prevent any attack by insect. However, in early 1960's it was discovered that DDT causes a lot of problems and

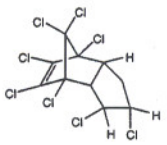
headaches due to its toxicity, extreme persistent and bioaccumulation in the environment [37]. This has led to the search of safer synthetic compounds such as chlorinated hydrocarbon (aldrin, dieldrin and chlordane). These synthetic compounds, however, caused more or less similar problems to DDT and their used have been greatly reduced or restricted.



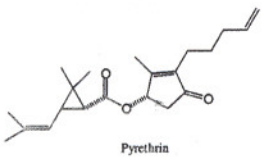
1,1,1-Trichloro-2,2-bis(*p*-chlorophenyl)ethane
DDT



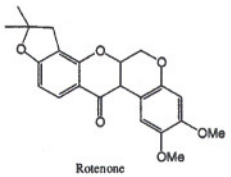
Aldrin



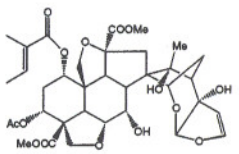
Chlordane



Pyrethrin



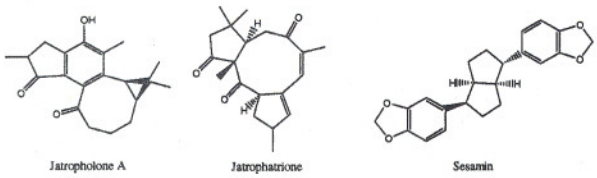
Rotenone

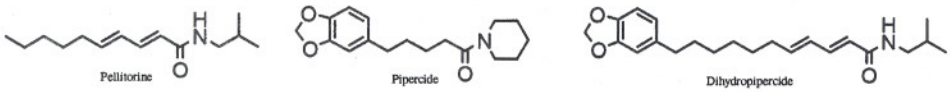


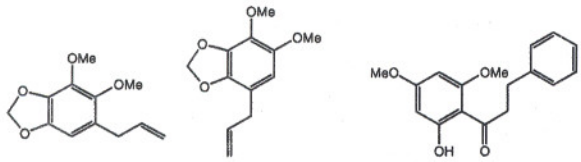
Azaditachtin

Thus, to overcome this and to find alternatives, a lot of works have been devoted to phytochemicals from plants which led to the discovery of such compounds as pyrethrum from *Chrysanthemum cinneriafolium* flowers, rotenone from *Derris elliptica* (pokok tuba), azadirachtin from *Azadirachta indica* (neem tree), nicotine, quassia and isobutylamides [38, 39].

One of the earlier methods we used to monitor the presence of presence of bioactive compounds was by using brine shrimp (*Artemia salina*) due to its reliability, reproducible, inexpensive and very rapid [40]. One of the plants we have tested by using this bioassay technique was *Piper nigrum* (black pepper) which showed very positive results and this was due to the presence of unsaturated isobutylamides such as pellitorine, pipercide and dihydropipercide as reported earlier by other workers and *Piper aduncum* [41]. To test the validity of this technique, the sample was also tested for ovicidal and larvicidal activity activities against mosquito larvae (*Aedes agytii*) and fruit-fly (*Drosophila melanogaster*) [42]. Another plant species *Zanthoxylum myriacunthum* (Rutaceae) also gave good results using this technique and comparable results were obtained by using third instar larvae of mosquito [43, 44].





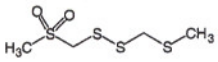


In the late eighties, when we started looking for bioactive compounds from plant sources, there were only a few readily available and simple assays at that time in the campus including piscicidal test against fish, contact insecticidal and larvae development inhibitor. In the piscicidal activity test, two readily available and easily handled fish species, *Labistes reticulaters* and *Tilapia mossambica* were used as the test organisms [45, 46]. A number of plant species have been investigated in detailed for their chemical components and biological activity using these fish species as the test organisms. One of the plants that gave very strong positive result was the extremely bitter *Tinospora crispa* (bekawali), but unfortunately no pure chemical components were able to be isolated from the extract. From another plant species, *Jatropha gossypifolia* (pokok jarak), which also gave good bioassay results, two pure diterpenoids jatropholone A and jatrophatrione were isolated and identified [47]. However, the two compounds were isolated in small quantity and insufficient to further test them against the fish species.

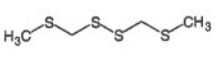
CONSTITUENTS AND BIOLOGICAL ACTIVITY OF NON-RUTACEOUS PLANTS

One of the more interesting plants we had been working with regards to their chemistry and bioactivity is from *Scorodocarpus borneensis* (Olacaceae). This is a big timber tree and locally the plant is known as 'pokok kulim' or garlic plant, with characteristic aroma of garlic [48]. Both the leaf and seed extracts gave very strong antifungal tests and bioassay-directed fractionation of the extract results in the isolation and identification of two sulphur-containing compounds, bis-(methylthiomethyl)disulphide and methylthiomethyl(methylsulfonyl)-methyldisulphide, scopodin (a new sesquiterpene), 8-isopropyl-5-methyl-2-napthoic acid and three new tryptamine-type of alkaloids

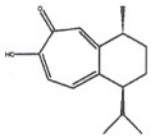
(scorodocarpine A, scorodocarpine B, scorodocarpine C) [49, 50]. bis-(Methylthiomethyl)disulphide appeared as the most active component and the major constituents of the seed extract (75%) and strongly inhibited the growth of pathogenic fungi. The compound also showed strong cytotoxic activity against CEM-SS, KU812F, UACC-62 and HT29 cell lines. CEM-SS cell line was found to be the most sensitive on the compound with CD_{50} value of 3.5 µg/ml. The crude extract and the pure isolated compound were formulated separately in external preparations by using commercial paraffin as excipient. Both preparations exhibited *in vitro* and *in vivo* drastic antifungal activities [51, 52].



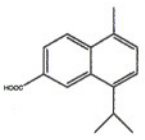
Methylthiomethyl(methylsulfonyl)methyldisulphide



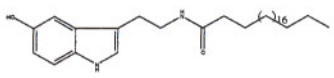
bis(Methylthiomethyl)disulphide



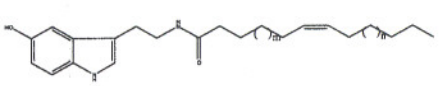
Scodopin



8-Isopropyl-5-methyl-2naphtoic acid

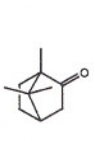


Scorodocarpine A



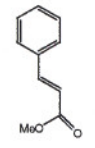
Scorodocarpine B; m=8, n=4
Scorodocarpine C; m=6, n=4

The other well-known medicinal plant species investigated for their chemical constituents and biological activities are the *Cinnamomum* species (Lauraceae), the commercially known cinnamom is obtain from members of the genus. Cinnamom oil, oleoresin and cinnamom sticks are primarily used in the food processing, cosmetics confectionary and pharmaceutical industries. The essential oils of nine species of *Cinnamomum* revealed the presence of monoterpenes, sesquiterpenes, phenylpropranoids and benzylic compounds such as methyl cinnamate, safrole, benzylbenzoate, linalool, terpinen-4-ol and camphor. These are commercially important chemicals in the flavor, food and pharmaceutical industries. The distribution and accumulation of compounds in different parts of the plants among different species may be used as a taxonomic marker for species identification. Bioassay-guided fractionation of the *Cinnamomum impressicostatum* and *C. pubescens* extracts revealed that the activity observed was due to the presence of methyl cinnamate [53-55]. Other compounds identified from the extracts are the 3,4-methylenedioxycinnamaldehyde, β-sitosterol, 3-(3,4-methylenedioxyphenyl)-2*E*-propenol, scoparone, pinoresinol etc.

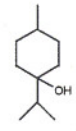


Camphor

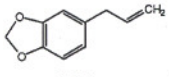
Linalool



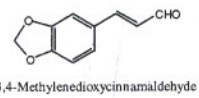
Methyl cinnamate



Terpinen-4-ol

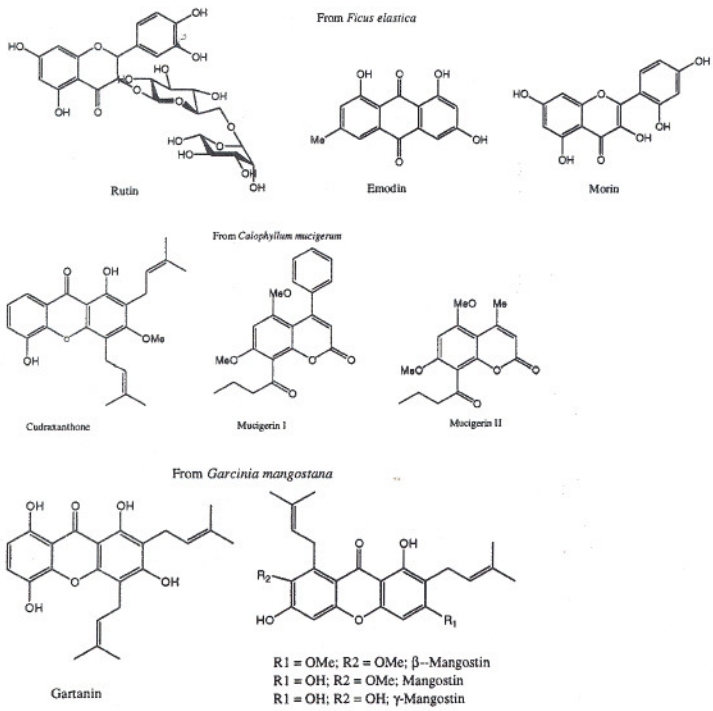


Safrole



3,4-Methylenedioxycinnamaldehyde

There are many other non-rutaceous plant species we have investigated in the past coupled of years such as Vitex [56, 57], Ficus [58], *Garcinia*, *Aegle* [59], *Ocimum* [60], *Goniothalamus* [61], *Calophyllum*, and *Citrus* [62] species which were not highlighted here. Some of the interesting compounds isolated with respect to their chemistry and biological activity are as given below. As mentioned earlier and the results of this work, it can be clearly seen that tropical flora offered a wide spectrum of interesting chemical structures. Only a fraction of these pure compounds have been tested against a very limited number of bioassay systems and more intense works need to be done in order to clearly exploit their potential.



CONCLUSION

Plants continue to be used world-wide for the treatment of various diseases and bioactive components as drug agents continue to be developed from these plants. In developed countries, high-throughput screening tests are used for bioassay-guided fractionation which will lead to the isolation and identification of the active principals. In turn this may develop into clinical agents either as the natural product or a synthetic modification or synthetic analogue with enhanced activity. Despite this development, herbal remedies have proved and continued to be popular as alternatives or complementary treatment of diseases. Thus, there is a need to evaluate these herbal preparation by using the current available protocols . In developing countries large number of population can not afford to

purchase pharmaceutical drugs and continue to use indigenous herbal preparation. There is a need to carry out proper research in order to investigate the quality, efficacy and safety of these herbal remedies.

Natural product will continue to supply banks of compounds and the focus of industry is currently on combinatorial synthesis for new drugs development. However, naturally occurring compounds which results from various biosynthetic pathways modified by evolution have a well established record as medicinal agents and offer a wide range of structural diversity. Thus, tropical plants will continue to contribute significant amount of these chemical diversity for the benefit mankind. Academics of course cannot match commercial pharmaceutical industry in the wide range of screens they conducted. However, they can use selective approach in selecting the plant species based on ethnobotanical knowledge and also collaborate with industry.

ACKNOWLEDGEMENTS

I wish to thanks and acknowledged Universiti Putra Malaysia for providing the facilities and environment for research activity; MOSTE under the Intensified Research in Priority Areas program (IRPA), International Foundation of Science (IFS), UNESCO and JSPS for providing financial supports. I also wish to thanks my coworkers and students for their invaluable involvement in this research:

Collaborators:
Dr. Mohd Aspollah Sukari, Dr. Taufiq-Yap Yun Hin, Prof. Nordin Hj Lajis, Dr. Abd Rahman Manas, Dr. Gwendoline Ee Cheng Lian, Dr. Khozirah Shaari, Prof. Abd.Manaf Ali, Prof. Sariah Meon, Dr. Hazar Bebe Mohd Ismail, Dr. Farediah Ahmad, Prof. Ruth Kiew, Prof. Peter Waterman, Prof. Norio Aimi, Dr. Chihiro Ito, Prof. Robert F. Toia.

Students (PhD and MSc)
Taufiq-Yap Yun Hin, Chew Yean Ling, Bonnie Tay, Redzuan Jamaluddin, Mohd Azlan Nafiah, Christphe Wiart, Shar Mariam Mohamad, Ratna Asmah Susidarti, Norazah Mohd Ali, Rosmiati, Ismiarni Komala, Najihah Mohd Hashim and the many final year undergraduate students.

REFERENCES

1. Farnsworth, N.R., Akerele, O. and Bingel A.S., 1985, Bull. World Health Org., 63, 965-981.

2. Cassady, J.M. and Douros, J.D., 1980, Anticancer agents based on natural product models, Academic Press, New York.

3. Sinha, S and Jain, S. 1994, Natural products as anticancer agents, *Prog. Drug Re.*, 42, 53; 43, 271.

4. Phillipson, J.D., 1999, New drugs from nature - it could be yew, Phytotherapy Research, 13, 2-8.

5. Dewick, M.P. 1996, Tumor inhibitor from plants. In: Trease and Evan's Pharmacognosy, 14th Ed. WB Saunders Co. Ltd., New York.

6. MacRae, W.D. and Towers, G.H.N., 1984, *Phytochemistry*, 23, 1207.

7. Cordell, G.A., 1993, The discovery of plant anticancer agents, Chem. Ind., 841.

8. Kinghorn, A.D. and Balandrin, M.F., 1993, Human medicinal agents from plants, ACS Symposium series, 534, ACS, Washington DC.

9. Kashman, Y., Gustafson, K.R., Fuller, R.W., Cardellina, J.H., McMahon, J.B., Currens, M.J., Buckeit, R.W., Hughes, S.H., Cragg, G.M. and Boyd, M.R., 1992, The calanolides: a novel HIV-inhibitory class of coumarin derivatives from tropical rain forest tree, Calophyllum lanigerum, *J. Med. Chem.*, 35(15), 2735-2743.

10. Soejarto, D.D., Cragg, G.M., Fuller, R.W., Cardellina, J.H. and Boyd, M.R., 1993, Challenges in developing a new drug from tropical rain forest plants, *Proceeding of the International Congress on the Industrial Utilization of Tropical Plants and the Conservation of Biodiversity*, February 15-19, Enugu, Nigeria.

11. M. Rahmani, M., Kiew, R., Lajis, N.H., Othman R. and Toia, R.F., 1985, A contribution to the phytochemical survey of Peninsular Malaysia, Pertanika, 8(3), 347-357.

12. Puonglux, D., Supavita, T., Verpoorte, R., and Phillipson, J.D., 1980, Alkaloids of Uncaria attenuata from Thailand, *Phytochemistry*, 19, 2013.

13. Rahmani, M., Toia, R.F. and Croft, K.D., 1989, The alkaloid constituents of *Hernandia nymphaefolia*, *J. Science Malaysiana*, 18(2), 45.

14. Rahmani, M., Ismail, H.B.M. and Toia, R.F., The chemistry of lignans and their distribution in the plant kingdom, *The 6th. National Seminar of the Natural Product Group*, June 1989, Universiti Teknologi Malaysia.

15. Rahmani, M., Toia, R.F. and Croft, K.D., 1995, Lignans from barks of Hernandia nymphaefolia and H. peltata, Planta Medica, 61, 487-488.

16. Rahmani, M., Toia, R.F., Ismail, H.B.M., Manas, A.R. and Takahashi, S., 1993, Lignans

constituents of tropical plants, *The 3rd. JSPS-VCC Seminar on Integrated Engineering*, Universiti Malaya.

17. Matsunaga, S., Rahmani, M., Ismail, H.B.M., Tanaka, R., Takaoka, Y., In, Y. and Ishida, T., 1993, 26-Nor-D:A-friedooeanene triterpenes from *Phyllanthus watsonii*, *Phytochemistry*, 32(1), 165.

18. Takaoka, Y., Tanaka, R., Mizutaru, H., Ishihara, Y., Matsunaga, S. and Rahmani, M., 1991, Chemical constituents of a Malaysian plant: *Phyllanthus watsonii*, *The 111th Annual Meeting of the Pharmaceutical Society of Japan*, March 1991, Tokyo, Japan.

19. Rahmani, M., Ismail, H.B.M. and Muthu, E., 1989, The structure of stemofoline from *Stemona tuberosa*, *ASEAN J. Sci. Tech. Development*, 6(2), 98.

20. Rahmani, M., Ismail, H.B.M. and Manas, A.R., 1990, Alkaloids constituents of two Malaysian plants, *Seminar and Workshop on Carbohydrates and Carbohydrate Containing Natural Products*, July 1990, University of Peradeniya, Sri Lanka.

21. Brophy, J.J., Rahmani, M., Toia, R.F., Croft, K.D. and Lassak, E.V., 1985, The volatile oils of *Euodia hortensis* forma *hortensis*, *Flavour and Fragrance J.*, 1, 7.

22. Rahmani, M., 1997, Chemical constituents and biological activities of natural products from Malaysian tropical plants, *International Symposium of Advanced Technology in Organo and biochemical Industries*, November 1997, Osaka Municipal Technical Research Institute, Osaka, Japan.

23. Rahmani, M., Chew, Y.L., Ismail,H.B.M., Sukari, M.A., Meon, S. and Aimi, N., 1998, 7-methoxyglycomaurin: a new carbazole alkaloid *from Glycosmis rupestris*, *Planta Medica*, 8, 780.

24. Chew Yean Ling, 1995, Chemical constituents of *Glycosmis calcicola* and *G. rupestris* (Rutaceae) and their biological activities, MSc Thesis, Universiti Putra Malaysia.

25. Greger, H., Hadacek, F., Hoffer, O., Wurz, G and Zechner, G., 1993, Different types of sulphur containing amides from Glycosmis chlorosperma, Phytochemistry, 32(4), 933-936.

26. Greger, H., Hoffer, O., Zechner, G.,Hadacek, F. and Wurz, G. 1994, Sulphones derived from methylthiopropenoic acid amides from *Glycosmis angustifolia*, *Phytochemistry*, 37(5), 1305-1310.

27. Shar Mariam Mohamed, 2000, Cytotoxic effects of methylgerambullin and bis(methylthiomethyl)disulphide on T-lymphoblastic leukemic cell line (CEM-SS), PhD Thesis, Universiti Putra Malaysia.

28. Rahmani, M., Taufiq-Yap, Y.H., Ismail, H.B.M., Sukari, M.A. and Manas, A.R., 1993, Microminutinin: a novel coumarin from *Micromelum minutum, Planta Medica*, 59, 93.

29. Rahmani, M., Taufiq-Yap, Y.H., Ismail, H.B.M., Sukari, M.A. and Waterman, P.G., 1994, New coumarins and dihydrocinnamic acid derivatives from two Malaysian populations of *Micromelum minutum, Phytochemistry*, 37(2), 561-564.

30. Taufiq-Yap, Y.H. and Rahmani, M., 1998, Microminutinin: a potential insect development inhibitor, *Tropical Biomedicine*, 15(3), 25.

31. Ratna Asmah Susidarti, 2002, Chemical constituents and biological activities of *Micromelum* and *Eugenia* species, PhD Thesis, Universiti Putra Malaysia.

32. Rahmani, M., Taufiq-Yap, Y.H., Sukari, M.A. and Ismail, H.B.M., 1996, Constituents of *Acronychia laurifolia, Fitoterapia*, 2, 180.

33. Sukari, M.A., Salim, W.S.W., Ibrahin, M.H., Rahmani, M., Aimi, N. and Kitajima, M., 1999, Phenantridine alkaloids from *Zanthoxylum myriacanthum, Fitoterapia*, 70, 197-199.

34. Sukari, M.A., Yeap, C.L., Rahmani, M., Hassan, F.H. and Silong, S., 1999, Chemical constituents from *Zanthoxylum myriacanthum (Rutaceae),Ultra Sci. Phy. Sci.*, 11(1), 96-99.

35. Sukari, M.A.,Salim, W.S.W., Ibrahim, N.H., Rahmani, M., Aimi, N. and Kitajima, M., 1998, Phenantradine alkaloids from Zanthoxylum myriacanthum (Rutaceae), Ultra Sci. Phy. Sci., 10(2), 66-69.

36. Sukari, M.A., Ahmad, K., Aimi, N., Kitajima, M., Rahmani, M., Ee, G.E.L. and Ahmad, F.H., 2001, Carbazole alkaloids from stem bark of *Murraya koenigii, ACGAC Chem Res. Comm.*, 13, 2-8.

37. Matsui, M. and Yamamoto, I., 1971, In Naturally Occurring Insecticides, ed. Jacobson, M and Crosy, D.G., Marcel Dekker Inc., New York.

38. Morgan, E.D. and Butterworth, J.H. 1968, J. Chem. Soc., *Chem Comm.*, 23.

39. Rembold, H., 1989, Azadirachtins: their structure ad mode of action, In Insecticides of plant origin, eds. Arnason, J.T., Philogene, B.J.R. and Morand, P., ACS Symposium Series 387, ACS, Washington DC.

40. Sukari, M.A., Rahmani, M., Desa, M.Z., Manas, A.R., Yusof, O., Ahmad, M.S. and Takahashi, S., 1989, Toxicity studies of some medicinal plants, *The 6th ASIAN Symposium on Medicinal Plants and Spices*, January 1989, Bandung, Indonesia.

41. Ahmad, F. and Rahmani, M., 1993, Chemical components of Piper *aduncum* Linn. (Piperaceae), *Pertanika J Sci. Technol.*, 1(2), 185-188.

42. Rahmani, M., Ismail, H.B.M., Ahmad, F., Sukari, M.A., and Manas, A.R., 1992, Screening of tropical plants for the presence of bioactive compounds, *Pertanika*, 15(2), 131.

43. Sukari, M.A., Rahmani, M., Ng, B.C., Haron, M.J., Ali, J.H. and Ahmad, F.B.H., 1996, Chemical constituents of the leaves of *Zanthoxylum acanthopodium* and its biological activity, *Orient J. Chem.*, 12(2), 135-136.

44. Sukari, M.A., Rahmani, M., Haron, M.J. and Takahashi, S., 1995, Allelophatic activity of essential oils of some plants on mung beans seedlings, *J. Sci. Malaysiana*, 4(2), 31.

45. Rahmani, M., Leong, T.Y. and Lajis, N.H., 1989, Toxicity studies of plant extracts on two species of fish, *Pertanika*, 12(2), 189.

46. Sukari, M.A., Rahmani, M., Manas, A.R. and Takahashi, S., 1992, Toxicity studies of plant extracts on insect and fish, *Pertanika*, 14(1), 41-44.

47. Rahmani, M., Ismail, H.B.M. and Leong, T.Y., 1990, Jatropholone and jatrophatrione from *Jatropha gossypifolia*, *Pertanika*, 13(3), 405.

48. Burkill, I.H. 1935, A dictionary of economic product of the Malay Peninsula, 2 Vols. Crown Agent for the Colonies, Reprinted, 1966, Ministry of Agriculture and Cooperative, Kuala Lumpur, Malaysia.

49. Kikue, K., Mika, M., Mika, U. and Akio, K, 1994, Antimicrobial compounds from Scorodocarpus borneensis, Bioscience, *Biotechnology and Biochemistry*, 58(2), 430.

50. Wiart, C., Martin, M-T., Awang, K., Hue, N., Serani, L., Laprevote, O., Pais, M. and Rahmani, M., 2001, Sesquiterpenes and alkaloids from *Scorodocarpus borneensis*, *Phytochemistry*, 58, 653-656.

51. Christophe Wiart, 2000, Antimicrobial and cytotoxic compounds from *Scorodocarpus borneensis* and *Glycosmis calcicola*, PhD Thesis, Universiti Putra Malaysia.

52. Wiart, C., M. Rahmani, A.M. Ali and M.A. Sukari, 2000, Chemical constituents, antimicrobial and cytotoxic activities of *Scorodocarpus borneensis* (Olacaceae), The 16th National Seminar on Natural Products, UPM, 24-25 Oct. 2000.

53. Nor Azah, M.A., Mastura, M., Kozirah, S., Rahmani, M and Ali, A.M., 2002, Chemical composition and antimicrobial activities of the essential oils of *Cinnamomum aureofulvum* Gamb., *Journal of Essential Oil Research*, 14, 135-138.

54. Mastura, M., M.A. Nor Azah, S. Khozirah, M. Rahmani and A.M. Ali, 1999, Anticandidal antidermatophytic activity of *Cinnamomum* species essential oils, *Cytobios*, 98, 17-23.

55. Nor Azah M.A., Rahmani, M., Ali, A.M., Khozirah, S., Ahmad, A.S. and Zoll Patah, M.F., 1999, Essential oil constituents of *Cinnamomum pubescens* Kochummen from Cameron Highlands, Malaysian Science and Technology Congress, Mingcourt Vista Hotel, Kuala Lumpur, 25-27 Oktober 1999.

56. Hassan, A.A., Rahmani, M., Sukari, M.A. and Ali, A.M., 2001, Antimicrobial and cytotoxic activity of cholesterol and b-sitosterol from chloroform extract of *Vitex quinata, Pertanika Journal of Science & Technology*, 9(2), 1-7.

57. Hassan, A.A., Rahmani, M., Sukari, M.A. and Ali, A.M., 2002, Isolation and characterization of the chemical constituents of the methanol extract of Vitex longisepala leaves and their antimicrobial activity, *J. Tropical Medicinal Plants*, 3(2), 155.

58. Hassan, A.A., Rahmani, M., Sukari, M.A. and Ali, A.M., 2002, Biological activity of certain chemical constituents in the leaves of *Ficus elastica, J. Tropical Medicinal Plants*, 3(2), 163.

59. Riyanto, S., Sukari, M.A., Rahmani, M., Ali, M.A., Aimi, N. and Kitajima, M., 2001, Alkaloids from Aegle marmelos (Rutaceae), *The Malaysian Journal of Analytical Sciences*, 7(2), 463-465.

60. Sukari, M.A., Rahmani, M., and Takahashi, S., 1995, Chemical constituents of stem bark of *Ocimum sanctum, Fitoterapia*, 116(6), 552.

61. Ee, G.C.L., Pang, Y.S., Rahmani, M. and Taufiq-Yap, Y.H., 2000, Bioactive styryllactones from Goniothalamus tapis, *Res. J. Chem. Environ.* 4(3), 7.

62. Taufiq-Yap, Y.H., Peh, T.H., Ee, G.C.L. and Rahmani, M., 2000, Chemical Investigation of *Acalypha indica* (Euphorbiaceae), *Oriental J. Chem.*, 16(2), 249.

63. Taufiq-Yap, Y.H., Peh, T.H., Ee, G.C.L, Ali, A.M., Rahmani, M., Sukari, M.A. and Muse, R., 2001, Chemical variability and some biological activities of leaf essential oils from five species of Malaysian *Citrus, Oriental Journal of Chemistry*, 17(3), 387-390.

SENARAI SYARAHAN INAUGURAL

1. **Prof. Dr. Sulaiman M. Yassin**
   The Challenge to Communication Research in Extension
   22 Julai 1989

2. **Prof. Ir. Abang Abdullah Abang Ali**
   Indigenous Materials and Technology for Low Cost Housing
   30 Ogos 1990

3. **Prof. Dr. Abdul Rahman Abdul Razak**
   Plant Parasitic Nematodes, Lesser Known Pests of Agricultural Crops
   30 Januari 1993

4. **Prof. Dr. Mohamed Suleiman**
   Numerical Solution of Ordinary Differential Equations. A Historical Perspective
   11 Disember 1993

5. **Prof. Dr. Mohd. Ariff Hussein**
   Changing Roles of Agricultural Economics
   5 Mac 1994

6. **Prof. Dr. Mohd. Ismail Ahmad**
   Marketing Management: Prospects and Challenges for Agriculture
   6 April 1994

7. **Prof. Dr. Mohamed Mahyuddin Mohd. Dahan**
   The Changing Demand for Livestock Products
   20 April 1994

8. **Prof. Dr. Ruth Kiew**
   Plant Taxonomy, Biodiversity and Conservation
   11 Mei 1994

9. **Prof. Ir. Dr. Mohd. Zohadie Bardaie**
   Engineering Technological Developments Propelling Agriculture into the 21st Century
   28 Mei 1994

10. **Prof. Dr. Shamsuddin Jusop**
    Rock, Mineral and Soil
    18 Jun 1994

11. **Prof Dr. Abdul Salam Abdullah**
    Natural Toxicants Affecting Animal Health and Production
    29 Jun 1994

12. **Prof. Dr. Mohd. Yusof Hussein**
Pest Control : A Challenge in Applied Ecology
9 Julai 1994

13. **Prof. Dr. Kapt. Mohd. Ibrahim Haji Mohamed**
Managing Challenges in Fisheries Development through Science and Technology
23 Julai 1994

14. **Prof. Dr. Hj. Amat Juhari Moain**
Sejarah Keagungan Bahasa Melayu
6 Ogos 1994

15. **Prof. Dr. Law Ah Theem**
Oil Pollution in the Malaysian Seas
24 September 1994

16. **Prof. Dr. Md. Nordin Hj. Lajis**
Fine Chemicals from Biological Resources: The Wealth from Nature
21 Januari 1995

17. **Prof. Dr. Sheikh Omar Abdul Rahman**
Health, Disease and Death in Creatures Great and Small
25 Februari 1995

18. **Prof. Dr. Mohamed Shariff Mohamed Din**
Fish Health : An Odyssey through the Asia – Pacific Region
25 Mac 1995

19. **Prof. Dr. Tengku Azmi Tengku Ibrahim**
Chromosome Distribution and Production Performance of Water Buffaloes
6 Mei 1995

20. **Prof. Dr. Abdul Hamid Mahmood**
Bahasa Melayu sebagai Bahasa Ilmu - Cabaran dan Harapan
10 Jun 1995

21. **Prof. Dr. Rahim Md. Sail**
Extension Education for Industrialising Malaysia: Trends, Priorities and Emerging Issues
22 Julai 1995

22. **Prof. Dr. Nik Muhammad Nik Abd. Majid**
The Diminishing Tropical Rain Forest: Causes, Symptoms and Cure
19 Ogos 1995

23. **Prof. Dr. Ang Kok Jee**
The Evolution of an Environmentally Friendly Hatchery Technology for Udang Galah, the King of Freshwater Prawns and a Glimpse into the Future of Aquaculture in the 21st Century
14 Oktober 1995

24. **Prof. Dr. Sharifuddin Haji Abdul Hamid**
Management of Highly Weathered Acid Soils for Sustainable Crop Production
28 Oktober 1999

25. **Prof. Dr. Yu Swee Yean**
Fish Processing and Preservation . Recent Advances and Future Directions
9 Disember 1995

26. **Prof. Dr. Rosli Mohamad**
Pesticide Usage: Concern and Options
10 Februari 1996

27. **Prof. Dr. Mohamed Ismail Abdul Karim**
Microbial Fermentation and Utilization of Agricultural Bioresources and Wastes in Malaysia
2 Mac 1996

28. **Prof. Dr. Wan Sulaiman Wan Harun**
Soil Physics: From Glass Beads To Precision Agriculture
16 Mac 1996

29. **Prof. Dr. Abdul Aziz Abdul Rahman**
Sustained Growth And Sustainable Development: Is there A Trade-Off 1~'or Malaysia
13 April 1996

30. **Prof. Dr. Chew Tek Ann**
Sharecropping in Perfectly Competitive Markets . A Contradiction in Terms
27 April 1996

31. **Prof. Dr. Mohd. Yusuf Sulaiman**
Back to The Future with The Sun
l8 Mei 1996.

32. **Prof. Dr. Abu Bakar Salleh**
Enzyme technology: The Basis for Biotechnological Development
8 Jun 1996

33. **Prof. Dr. Kamel Ariffin Mohd. Atan**
The Fascinating Numbers
29 Jun 1996

34. **Prof. Dr. Ho Yin Wan**
Fungi. Friends or Foes
27 Julai 1996

35. **Prof. Dr. Tan Soon Guan**
Genetic Diversity of Some Southeast Asian Animals: Of Buffaloes and Goats and Fishes Too
10 Ogos 1996

36. **Prof. Dr. Nazaruddin Mohd. Jali**
Will Rural Sociology Remain Relevant In The 21st Century
21 September 1996

37. **Prof. Dr. Abdul Rani Bahaman**
Leptospirosis - A Mode/ for Epidemiology, Diagnosis and Control of Infectious Diseases
16 November 1996

38. **Prof. Dr. Marziah Mahmood**
Plant Biotechnology - Strategies for Commercialization
21 Disember 1996

39. **Prof. Dr. Ishak Hj. Omar**
Market Relationships in The Malaysian Fish Trade: Theory and Application
22 Mac 1997

40. **Prof. Dr. Suhaila Mohamad**
Food and its Healing Power
12 April 1997

41. **Prof. Dr. Malay Raj Mukerjee**
A Distributed Collaborative Environment for Distance Learning Applications
17 Jun 1998

42. **Prof. Dr. Wong Kai Choo**
Advancing the Fruit Industry in Malaysia: A Need to Shift Research Emphasis
15 Mei 1999

43 **Prof. Dr. Aini Ideris**
Avian Respiratory and Immunosuppressive Diseases - A Fatal Attraction
10 Julai 1999

44. **Prof. Dr. Sariah Meon**
Biological Control of Plant Pathogens: Harnessing the Richness of Microbial Diversity
14 Ogos 1999

45. **Prof. Dr. Azizah Hashim**
The Endomycorrhiza: A Futile Investment?
23 Oktober 1999

46. **Prof. Dr. Noraini Abd. Samad**
Molecular Plant Virology: The Way Forward
2 Februari 2000

47. **Prof. Dr. Muhamad Awang**
Do We have Enough Clean Air to Breathe?
7 April 2000

48. **Prof. Dr. Lee Chnoong Kheng**
Green Environment, Clean Power
24 Jun 2000

49. **Prof. Dr. Mohd. Ghazali Mohayiddin**
Managing Change in the Agriculture Sector : The Need for Innovation Educational Initiatives
12 Januari 2002

50. **Prof. Dr. Fatimah Mohd. Arshad**
Analisis Pemasaran Pertanian Di Malaysia : Keperluan Agenda Pembaharuan
26 Januari 2002

51. **Prof. Dr. Nik Mustapha R. Abdullah**
Fisheries Co-Management: An Institutional Innovation Towards Sustainable Fisheries Industry
28 Februari 2002

52. **Prof. Dr. Gulam Rusul Rahmat Ali**
Food Safety: Perspectives and Challenges
23 Mac 2002

53. **Prof. Dr. Zaharah Binti A. Rahman**
Nutrient Management Strategies for Sustainable Crop Production in Acid Soils: The Role of Research using Isotopes
13 April 2002

54. **Prof. Dr. Maisom Abdullah**
Productivity Driven Growth: Problems & Possibilities
27 April 2002

55. **Prof. Dr. Wan Omar Abdullah**
Immunodiagnosis and Vaccination for Brugian Filariasis: Direct Rewards from Research Investments
6 Jun 2002

56. **Prof. Dr. Syed Tajuddin Syed Hassan**
Agro-ento Bioinformation: Towards the Edge of Reality
22 Jun 2002

57. **Prof. Dr. Dahlan Ismail**
Sustainability of Tropical Animal- Agricultural Production Systems: Integration of Dynamic Complex Systems
27 Jun 2002

58. **Prof. Dr. Ahmad Zubaidi Baharumshah**
The Economics of Exchange Rates in the East Asian Countries
26 October 2002

59. **Prof. Dr. Shaik Md. Noor Alam S.M. Hussain**
Contractual Justice in Asean: A Comparative View of Coercion
31 October 2002

60. **Prof. Dr. Wan Md. Zin Wan Yunus**
Chemical Modification of Polymers: Current and Future Routes for Synthesizing New Polymeric Compounds
9 November 2002

61. **Prof. Dr. Annuar Md Nassir**
Is The KLSE Efficient? Efficient Market Hypothesis vs Behavioural Finance
23 November 2002

62. **Prof. Ir. Dr. Radin Umar Radin Sohadi**
Road Safety Interventions in Malaysia: How Effective Are They?
21 Februari 2003

63. **Prof. Dr. Shamsher Mohamad**
The New Shares Market: Regulatory Intervention, Forecast Errors and Challenges
26 April 2003

64. **Prof. Dr. Han Chun Kwong**
Blueprint for Transformation or Business as Usual? A Structurational Perspective of The Knowledge-Based Economy in Malaysia
31 Mei 2003