fruits of *Morinda ellliptica*

Syarahan INAUGURAL

oleh

PROF. DR. MD. NORDIN HJ. LAJIS
Fakulti Sains dan Pengajian Alam Sekitar
Universiti Pertanian Malaysia

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PROF. DR. MD. NORDIN HJ. LAJIS

Bertajuk

FINE CHEMICALS FROM BIOLOGICAL RESOURCES: THE WEALTH FROM NATURE

21 JANUARI 1995

Dewan Persidangan
Pusat Pengembangan Dan Pendidikan Lanjutan
Universiti Pertanian Malaysia

MD. NORDIN BIN HJ. LAJIS

Dilahirkan di Kampung Bukit Nibong, Paya Dalam pada tahun 1952, Md. Nordin Hj. Lajis telah mendapat pendidikan awal di Sekolah Kebangsaan Paya Dalam, Sekolah Menengah Kebangsaan Lelaki Bandar Melaka dan Sekolah Menengah Alam Shah, Kuala Lumpur.

Beliau telah mendapat Ijazah Sarjana Muda Sains dari UKM pada tahun 1974 dan Ijazah Kedoktoran (Ph.D.) dalam bidang Sintesis Organik dari University of Georgia, U.S.A. pada tahun 1979.

Beliau telah dilantik menjadi tutor di Universiti Pertanian Malaysia pada tahun 1974 dan menjadi pensyarah sekembalinya dari menyelesaikan pengajian Ph.D. nya.

Dalam bidang pentadbiran beliau telah dilantik sebagai Ketua Jabatan Kimia pada tahun 1986 hingga 1988 dan pada tahun 1991. Beliau mula menjadi Timbalan Dekan Fakulti Sains dan Pengajian Alam Sekitar pada November, 1991. Beliau telah dilantik sebagai Prof. Madya pada 1988.

Di samping menjalankan tugas pengajaran, penyelidikan dan pentadbiran di Universiti beliau juga aktif dalam bidang Pembangunan Penyelidikan Kimia Sebatian Semulajadi pada peringkat Kebangsaan dan peringkat Serantau. Kegiatan beliau ini telah menyebabkan beliau dilantik sebagai ***National Point of Contact Representative for the UNESCO Regional Network for the Chemistry of Natural Products in Southeast Asia*** dan sekali gus menjadi Pengerusi Jawatankuasa Kebangsaan bagi Rangkaian Serantau tersebut. Pada tahun 1989 beliau menjadi ***Executive Secretary for the UNESCO - Regional Network for the Chemistry of Natural Products in Southeast Asia.***

Untuk meningkatkan lagi penyelidikan dalam bidang sebatian semulajadi di peringkat Kebangsaan, beliau telahpun mengasaskan Persatuan-Persatuan Semulajadi Malaysia bagi tujuan untuk menyelaras aktiviti yang selama in dilakukan oleh Jawatankuasa Kebangsaan. ***The Eighth Asian Symposium*** *on Medicinal Plants Spices and Other Natural Products (ASOMPS VIII)* adalah aktiviti pertama Persatuan ini yang beliau pengerusikan.

Bidang penyelidikan yang diminati oleh beliau pada asasnya adalah Kajian Kimia ke Atas Sebatian Aktif dan ini termasuk kajian sintesis dan struktur. Penyelidikan beliau telah dibiayai oleh **Majlis Penyelidikan dan Kemajuan Sains Negara (MPKSN)** serta ***The International Foundation for Science***. Beliau telah menerbitkan 55 kertas penyelidikan dalam jurnal yang diadili. Di samping itu beliau juga menerbitkan 2 buah buku karya asli dan menterjemahkan sebuah buku teks. Oleh kerana minat beliau dalam perkembangan bahasa menyebabkan beliau dilantik sebagai **Pengerusi Jawatankuasa Istilah Kimia**, Dewan Bahasa dan Pustaka dan dengan itu menjadi ahli bersekutu kepada Jawatankuasa Tetap Bahasa Melayu serta terlibat dengan Majlis Bahasa Brunei, Indonesia dan Malaysia (MABBIM). Dalam pembangunan pendidikan beliua adalah **ahli Lembaga Penasihat dan Penilai Program *Diploma in Science***, ITM di samping menjadi ahli Jawatankuasa Penyemakan Sukatan Pelajaran STPM.

FINE CHEMICALS FROM BIOLOGICAL RESOURCES: THE WEALTH FROM NATURE

Introduction :

Man has exploited plants, animals and other microorganisms since the beginning of civilization for a great variety of purposes. In addition to providing food, clothing, fuel and timber, these bioresources also produce fine chemicals which have found widespread use as medicines, insecticides, fragrances, pigments etc. With the advent of biotechnology particularly in the field of genetic engineering and cell culture the interest to search for high value fine chemicals resurges due to the possibility of producing the desired products in more efficient, economical and environmental friendly manner.

The value of the global trade in plant-based pharmaceuticals alone is currently estimated at around 43 USD billion per year. The growing inclination of most people to prefer natural than unnatural or synthetic products, boosts further the potential of developing commercial products from natural sources.

The search for fine natural products from plants has been pursued since prehistoric times. Despite this, the interest in the discovery of new products still persists even today. There may be two major reasons why this is true. Firstly, historically plants have yielded numerous important lead structures for development, and secondly, only less than 10% of the world's 250,000 plants species have been investigated for more than one biological activities.

It is almost impossible to discuss the whole spectrum of contribution of natural products to human life in this lecture and therefore I will only cover the two most important areas in which natural products has widely been utilized.

Natural Products In Medicine and Related Fields:

Use of drugs is one of the important human defence strategies in maintaining good health. At present there are approximately 15,000 prescriptions containing one or more ingredients available in the market and the estimate on the number of non-prescription products varies from 100,000 to 1.5 million. Such enormous number unfortunately are still insufficient for consumers and physicians. The first reason was that there has not a single *perfect drug* been developed - the drug that has absolute specificity in its action, helps all persons with disease, has no side effects, and is completely non-toxic. Some good drugs such as penicillin suffer from being considered perfect drugs because certain resistant bacterial strains have progressively developed and about 10 per cent of the total population is allergic to it[1]. Discovery of new diseases such as AIDS and cancer add to the demand for new drugs.

Although the majority of drugs prescribed today are of synthetic origin, some 25 percent of them are derived from higher plants while a further 12 percent are from microbial sources. Of course, some of these pharmaceuticals are of complex molecules and would therefore be almost impossible to replace synthetically due to various constraints. These include low yield, high cost, complexity in chemical conversion and the need to obtain the compound in high purity.

Economically plant derived products contribute multimillion dollar profits to international pharmaceutical industries[(1,2,3)]. The annual sale of vincristine and vinblastine alone runs to about 100 million USD world wide. Some of the most common pharmaceuticals derived from plants and microorganisms are listed in Table 1.

Currently there is a growing interest in the field of marine pharmaceuticals. The earliest discovery of modern drugs from marine organisms may be traced back to the isolation of cephalosporin-C from *Cephalosporium acrimonium* [(4)]. Several algal toxin such as *Gonyaulax* toxin, saxitoxin and mytilotoxin have also been isolated from marine algae. These are among the most toxic compounds known to man which has pharmacological potency of more than

10^5 times than local anaesthetics such as procaine[5]. Quite recently the active principle of the red algae *Dignea simplex* was isolated and identified as kainic acid (2-carboxy-3-carboxymethyl-4-isopropenylpyrrolidone) and now is being

Table 1. Some Pharmaceuticals of Plants Origin.

Pharmaceuticals	Sources
Steroids from diosgenin	*Dioscorea deltoides*
Codeine	*Papaver somniferum*
Atropine/hyoscyamine	*Hyoscyamus niger*
Reserpine	*Rauwolfia serpentina*
Digoxin	*Digitalis lanata*
Digitoxin	*Digitalis purpurea*
Scopolamine	*Datura metel*
Pilocarpine	*Pilocarpus jabonandi*
Vincristine and vinblastine	*Catharanthus roseus*
Ephedrine	*Ephedra sinica*
Colchicine	*Colchicum autumnale*
Artemisinin	*Artemisia annua*
Taxol	*Taxus brefolia*
Yuehchukene	*Muraya paniculata*
Callonolide A	*Callophyllum lanigerum*

widely used clinically as a vermifuge and anthelmintic. It is interesting to note that this discovery was also based on the knowledge in folk medicine[2]. The interest in marine chemistry is currently extended further into the study of marine bacterial metabolites. Some other interesting compounds from the standpoint of chemistry and bioactivity have been discovered and their potential uses in chemotherapy seem to be promising[6].

The progress made in biotechnology has unveiled yet another potential exploitation of natural products in pharmaceutical industry. A multidisciplinary approach incorporating chemistry, biology, pharmacy and biochemistry have allowed the enhancement of product yields through tissue culture and genetic manipulation of cells[7].

Bioactive Natural Products Discovery Program:

The work involved in the discovery of bioactive natural products is like searching for a golden needle in a hay-stack. The statistics of the chances of discovering the *big hit* varies from one in 2000 to one in 10,000. The cost for developing a drug is also quite high with the conventional estimate running from 50 to 100 million USD. These, however, have not deterred many multinational pharmaceutical firms from embarking into new drugs discovery programs in view of the potential returns once a *big hit* is struck.

A research program directed at discovering new bioactive natural products requires a highly integrated and multidisciplinary approach. The very preliminary step is the selection of plants or organisms worthy of further investigations for the specific purposes. There are basically five systematic approaches for the selection of plants that may contain new biological agents : the random, the taxonomic, the chemotaxonomic, the information managed and the ethnomedical. In the random approach, all available species are collected, irrespective of prior knowledge and experience. In the taxonomic approach, plants of predetermined taxa deemed to be of interest are sought from diverse locations. In the chemotaxonomic approach, a particular compound class, e.g. isoquinoline alkaloid, may be considered as being of biological interest, and plants thought likely to have related compounds are collected. In the information-managed approach, those plants of proven biological activity which may likely contain unknown active agents are collected in the hope of discovering novel bioactive compounds.

In the ethnomedical approach, oral and written information on the medicinal use of the plants are collected and evaluated and plants of interest are collected. For each of the collection strategies, the most rational procedure is to test the material in a range of bioassays. Plants which give good leads are then prioritized, and those regarded as most active are subjected to bioassay-directed fractionation procedures for the isolation and identification of the active principle(s). Serendipity can sometimes contribute to a discovery program. Collection based on one bioactivity or ethnomedical record of the plant leads to the discovery of another bioactivity of commercial significance. A very classical example of this is the discovery of vincristine and vinblastine for the treatment of leukemia. *Catharanthus roseus* which produces the two drugs were initially studied for its traditional use in treatment of diabetes. For the purposes of new drug discovery from plants, it is believed that a combination of the ethnomedical and the information management approaches was supposed to be the most effective.

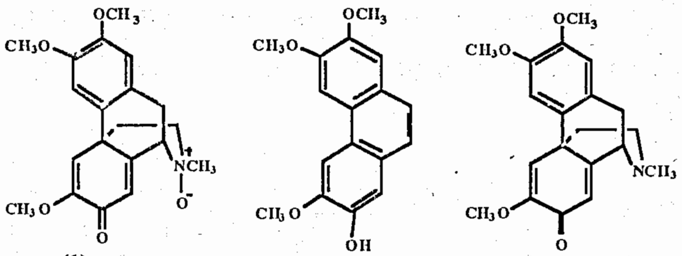
Ethnic folklore or empirical therapeutic uses of plant parts have often provided the early indication of the possibility in discovering some pharmacologically active substance from it. Application of the ethnomedical approach to a discovery program requires both the collection and prioritization of existing ethnomedical, chemical, biological and clinical data so that plant collection can be directed towards those viewed to be most likely to yield interesting new compounds for potential development. This may be achieved for a given biological activity by gathering information or data which can represent plants which have been studied for their active principles, ethnomedically reported plants with that or related biological activity, and plants for which a biological activity has been experimentally established, but from which no active principle has been isolated. Comparison of these data indicates a group of plants which have or are reported ethnomedically to have, a relevant biological activity, but from which no active compound has been obtained. The systematic collection of the listed plants is then executed.

In a bioactivity guided isolation work, commonly a series of compounds having closely related structure with the active principle(s) are at the same time isolated, thus allowing the researcher to carry out structure-activity relationship investigation. For the same purpose chemical transformation from the isolated product or total synthesis from remote chemical origin may be undertaken in order to have adequate representative of the series. As shown in several instances, the parent compounds or the so-called *lead compounds* are sometimes not satisfactory as it stands and the studies on structure activity relationship allow the best selection of candidates to be developed. In some cases plant isolated substances may be used as precursor for the synthesis of the selected drug.

The research related to the discovery of new products from natural sources at Universiti Pertanian Malaysia was undertaken due to several reasons. Being located in one of the mega-diverse region, our country stores a large number of species of flora and fauna, each of which may be equated to a working chemical plant consistently producing a unique chemical pool due to its unique genetic make-up. Some of these chemical make-ups are of no comparison to the synthetic counterparts and many are almost impossible to synthesize through conventional synthetic procedures. The rich cultural heritage of the Malaysian people also stores a vast knowledge on the traditional and practical uses of these biological resources. These uses have already undergone field trials through generations and therefore the efficacy of the materials used should certainly have some relevance to the modern scientific reasonings. In addition to creating new economic resources to the country discovery of valuable materials from our biological resources, it can also generate awareness among the general public on the value of these resources. This will in turn encourage them to conserve these biological resources and at the same time the environment.

Some of the approaches mentioned earlier have been adopted in selecting our research subjects. During the early period of development of research in natural products chemistry, selection of plants based on their alkaloid contents was carried out. Further prioritization was made according to their use in traditional medicine or other claims. The reasons for our interest in the alkaloids of these plants are firstly, due to the fact that most alkaloids have shown some biological activities and used widely in modern medicines, and secondly, alkaloids are basic compound and therefore its separation from other non-basic components is rather simpler than other components. It is therefore a good teaching exercise for the beginner students. This has led to a number of phytochemical screening exercises carried out from 1983 to 1987 covering several areas in peninsular Malaysia. A total of 746 plants samples have so far been screened for alkaloids with approximately 10 percent of them showing the presence of alkaloids.

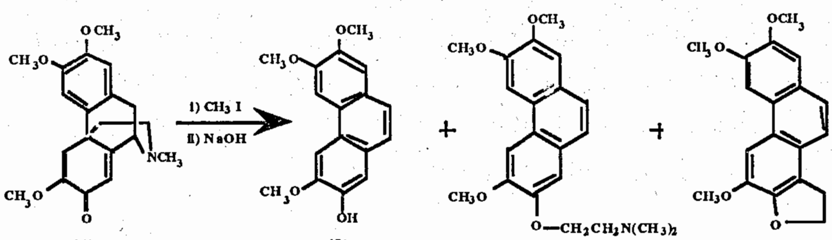
The study on *Alseodaphne perakensis* (Lauraceae) has led to the isolation of a new alkaloid assigned as sebiferine *N*-oxide **(1)**[8], a compound which was not previously isolated from plant called perakensol **(2)**[9], and a major morphine alkaloid, *N*-methyl-2,3,6-trimethoxymorphinandien-7-one (sebiferine) **(3)**[10]. Further pharmacological screening of the major alkaloid has shown a number of interesting activities including uterine stimulant, hypotensive, decrease of motor activity and analgesic.



(1) (2) (3)

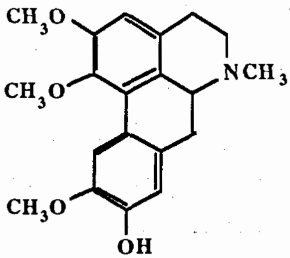
A suggestion by Battersby that morphinandienone may infact a precursor in the biogenesis of dibenzoazonine alkaloid, protostephanine, attracted our attention to investigate the generality of this idea(11). Thus, sebiferine was reduced to *N*-methyl-2,3,6-trimethoxymorphinandien-7-ol and then allowed to stand in acidic methanol. The postulated rearrangement did also occur in our system but solvolytic substitution products appeared to be the competing reaction.

The isolation of perakensol in the basic fraction of the crude extract raised a question whether this compound is in fact an artifact derived from the degradation of the tertiary salt of sebiferine. This possibility was considered in view of the previous report on the degradation of a similar molecular system. The presence of perakensol in *A. perakensis* was however confirmed by repeating the extraction and isolation procedures in a controlled manner. The degradation of sebiferine *N*-methiodide was also carried out, but to our surprise we isolated other interesting by-products **(4)** and **(5)** in addition to the major product, perakensol.



(1) (2) (4) (5)

Further investigation on lauraceous plant, *Lindera pipericarpa* has shown the generality of the chemotaxonomic relationship of this plant family in producing benzylisoquinoline-derived alkaloids. Three benzylisoquinoline alkaloids have been isolated and they were identified as *N*-methyllaurotetanine **(6)**, isocorydine **(7)** and nor-isocorydine **(8)**[12]. Benzylisoquinoline alkaloid was also isolated from *Cyclea laxiflora* in the form of an antiviral compound, dicentrine **(9)**[13].



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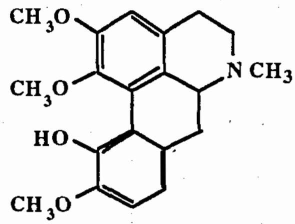

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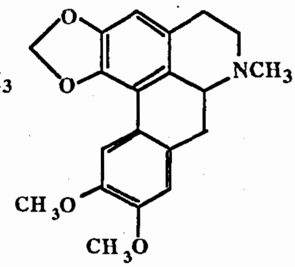

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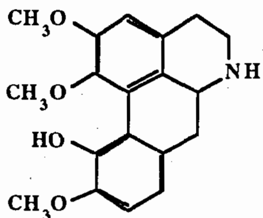
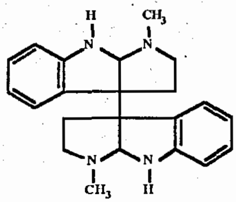


(8)

The chemical study on *Psychotria rostrata* was undertaken due to the high content of alkaloids and the claims of its uses in traditional remedies in treating constipation. A number of interesting pyrroloindoline alkaloids were isolated including (+)-chimonanthine **(10)**, (-)-calycanthine **(11)**, hodgkinsine **(12)**, calycosidine (13), and a major tetrameric pyrroloindoline, Quadrgemine B **(14)**[14]. Calycosidine was a novel alkaloid at the time of its isolation and the structure was confirmed through spectroscopic correlations. Pharmacological screenings showed that Quadrgemine B is cytotoxic towards human carcinoma epithelial (Hep-2) cells but rather non-toxic towards human lymphocytes. The compound also kills *S. aureus* and *E. coli*[15].



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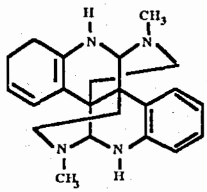

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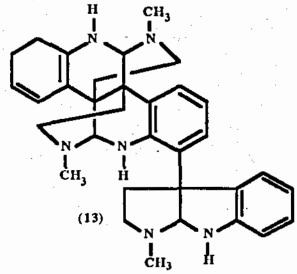

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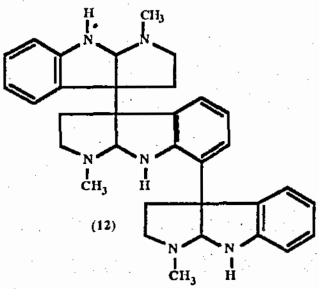

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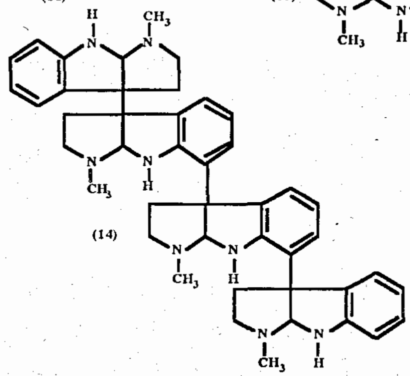

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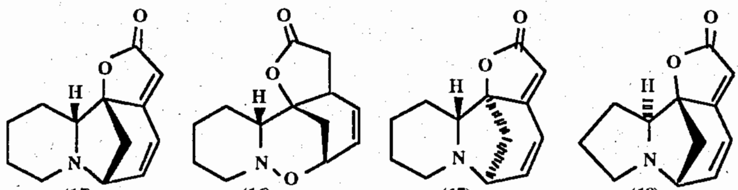
Our investigation on *Breynia coronata,* a large shrub collected in Langkawi Island resulted in the isolation of two securinega alkaloids, viroallosecurinine **(15)** and a new alkaloid, *ent*-phyllanthidine **(16)**[16]. Another study conducted on the same species collected in Sungai Besi, Selangor surprisingly gave different results. Three compounds related to but not the same as those previously isolated were identified. These include securinine **(17)**, *ent*-norsecurinine **(18)** and virosecurinine **(19)**. These results suggested that the two plant samples are of different genetic variety or if they are of genetically the same, the geographic location or the soil conditions must have altered the normal biogenetic pathways. It is interesting to note that securinine has reportedly been used clinically for the treatment of paralysis. A study on the effect of ionic and nonionic miscelles on the rate of hydroxide ion-catalysed hydrolysis of securinine has also been conducted with the view of exploring the potential of using miscelles as the drug carrier[17].



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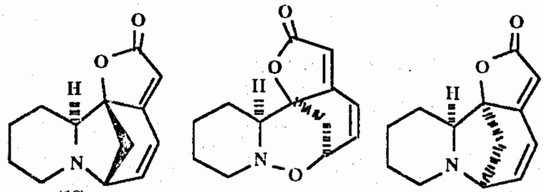
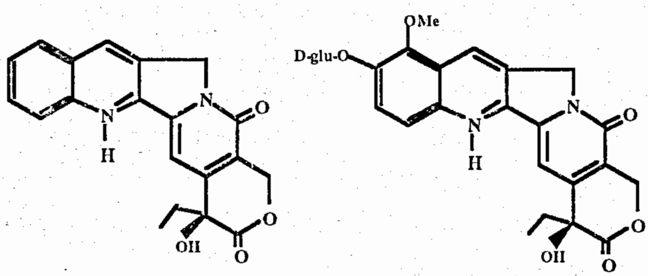
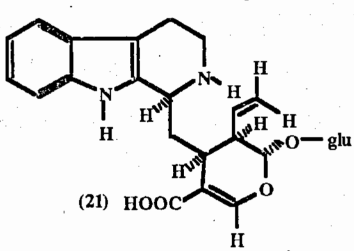


(19)

A recent report on the use of camptothecin **(20)** in the treatment of cancer has generated our interest in investigating a shrub from the genus *Ophiorrhiza* which are found in our forests. Plants from this genus were known to contain indole alkaloids which is the basic skeleton of camptothecin. Our study on *Ophiorrhiza communis* and *Ophiorrhiza tomentosa* resulted in the isolation of strictosidinic acid **(21)** and harman **(22)**(18). Strictisidinic acid is infact the precursor for the biogenesis of camptotheca alkaloids. A study on *Ophiorrhiza ferruginea* however gave us dihydroakagerine **(23)**, tetrahydroakagerine **(24)**, 3,14-dihydrodecussine **(25)** and a quaternary alkaloid isomalindine **(26)**(19).





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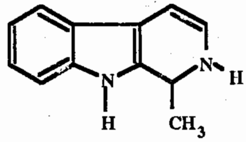

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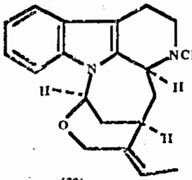

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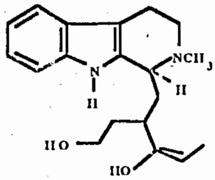

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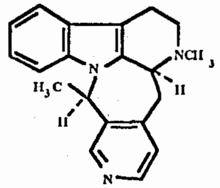

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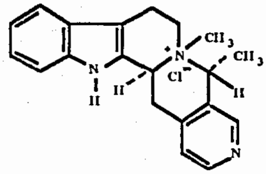

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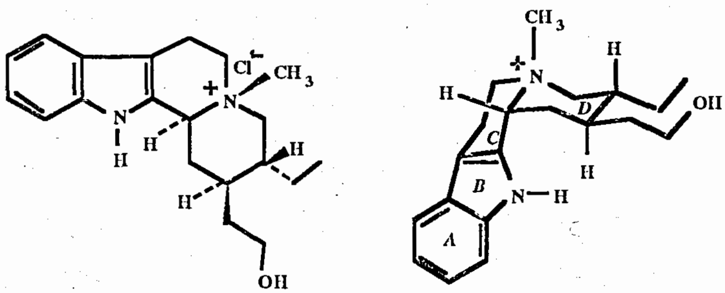
Further search for camptotheca alkaloids was conducted by the study of the alkaloids of *Lerchea bracteata,* a plant used for the treatment of skin infection. A quaternary corynathe' alkaloid, dihydro-3-*epi*-corynantheol methochloride (lercheine) **(27)** was isolated and a preliminary study showed that it inhibits bacterial growth(20).



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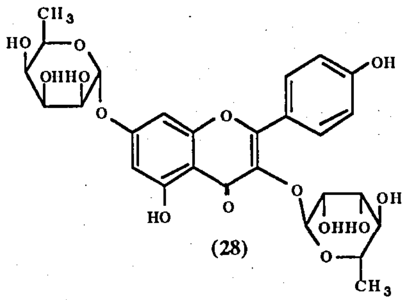
Our interest in *Hedyotis* plants began when we realised that many of the species are widely used by the Chinese and the Malays in their traditional remedies. *Hedyotis* are herbaceous plant which commonly grow as a weed in most lowland areas. Some 35 of 180 species of *Hedyotis* worldwide are found in peninsular Malaysia. Chemically, *Hedyotis* are known to produce a great variety of compounds including irridoid-glycosides, anthraquinones, phytosterols, sesquilignans and even alkaloids. We investigated three species and isolated several flavonoid-glycosides as well as some phytosterols. *Hedyotis verticillata* is found to contain kaempferitrin **(28)** and ursolic acid **(29)**(21) while *H. herbacea* contains kaempferol-3-*O*-rutinoside **(30)**, kaempferol-3-*O*-arabinopyranoside **(31)**, quercetin-galactoside **(32)** and ursolic acid(22). Kaempferitrin and ursolic acid seem to be rather toxic towards brine shrimp (*Artemia salina*) larvae as well as anti-bacterial. The study on *H. dichotoma* gave us isovitexin **(33)** and ursolic acid as the major constituents. Isovitexin was found to be fungicidal(23). Our studies therefore showed that the

Malaysian species invariably contain flavonoid-glycosides in addition to phytosterols. Several other flavonoids have also been isolated from other plants including luteolin **(34)** from *Vitex ovata*[24], hispidulin **(35)** from *Clerodendron oblongifolium*[25], and 2'-hydroxy 4,4',6'-trimethoxychalcone **(36)** and 5,7,4'-trimethoxyflavanone **(37)** from *Orophea polycarpa* [26].



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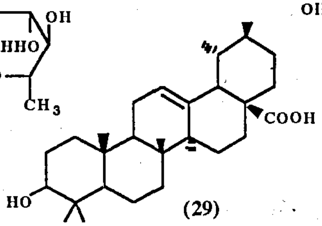

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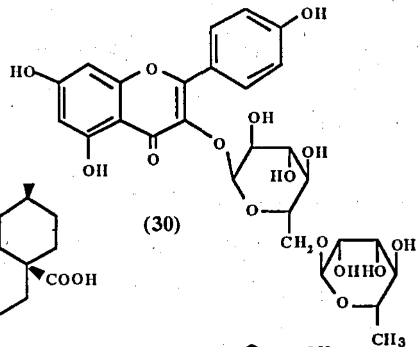

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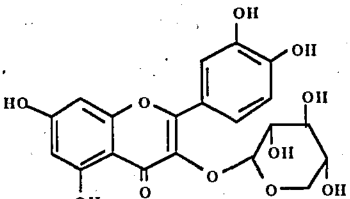

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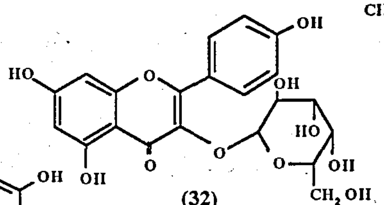

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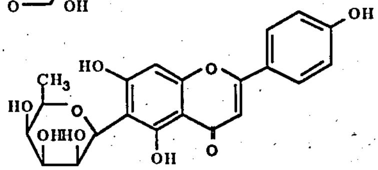

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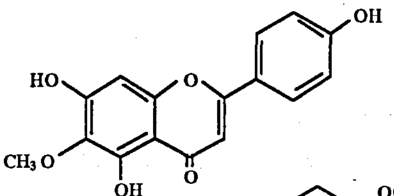

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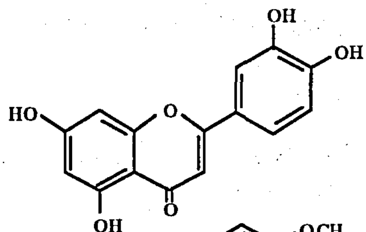

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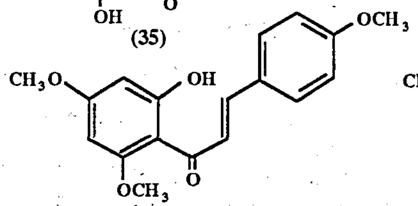

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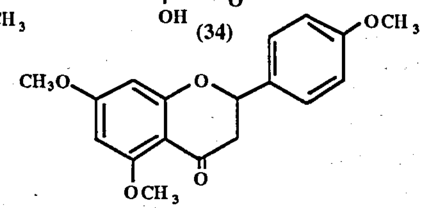

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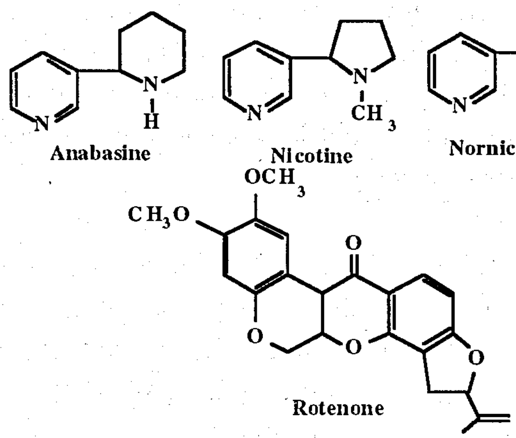
Although statistically the average rate of *hit* in bioprospecting expeditions is known to be low, we believe the chances of discovery could be improved if many bioassay systems are available to test the bioactivities of our plant or other biological extracts. Thus, collaboration with other experts interested in carrying out the bioassays of natural products and related areas is consistently pursued. Currently, several bioassay systems are available in our lab and other associated laboratories and bioassays of plants or other biological extracts are routinely conducted. These include assays for anti-bacterial and anti-fungal activities, anti-viral and anti-tumour activities, and brine shrimp (*Artemia salina*) toxicity test. Plants showing strong bioactivities are selected for further investigation. Several plant species are now under investigation from the results of these bioassays. *Morinda elliptica* , a shrub or small tree commonly growing in the newly developed areas or in bushes has shown several interesting activities including anti-bacterial, anti-fungal, anti-viral and cytotoxic towards cervical and breast carcinoma cells. Several anthraquinones have now been isolated and characterized and the bioactivities being evaluated. Other plants being investigated for their anti-microbials and anti-viral activities include *Vitex ovata*, *Hedyotis nudicaulis* and *Bixa orellana.*

Discovery of bioactive compounds based on *in vitro* or *in vivo* bioassays is the beginning of a drug development stage. General toxicity, clinical trials, bio-optimization, alternative approaches to production of the bioactive compounds including synthesis, agronomy and cell cultures *etc.* will normally follow. Some of these activities are now initiated within and outside the University.

Natural Products In Agriculture:

Insect pests have been one of the concerns in agriculture. Modern societies rely quite heavily on the use of pesticides for their agronomic needs particularly in plant protection. The discovery of DDT after the second world war which was initially thought to be the universal answer to insect control, proved to be disastrous. Rachel Carson's *Silent Spring* signalled the elimination of DDT's world wide use due to its extreme persistence, toxicity, bioaccumulation and tendency to cause malignancy(27). Frantic search for *safer* synthetics that followed resulted in the introduction of newer chlorinated hydrocarbons (aldrin, dieldrin, chlordane and heptachlor) which also proved to be unduly toxic, ecologically disastrous or induced insect resistance. In the search for safer alternatives, attention has turned to botanicals[28].

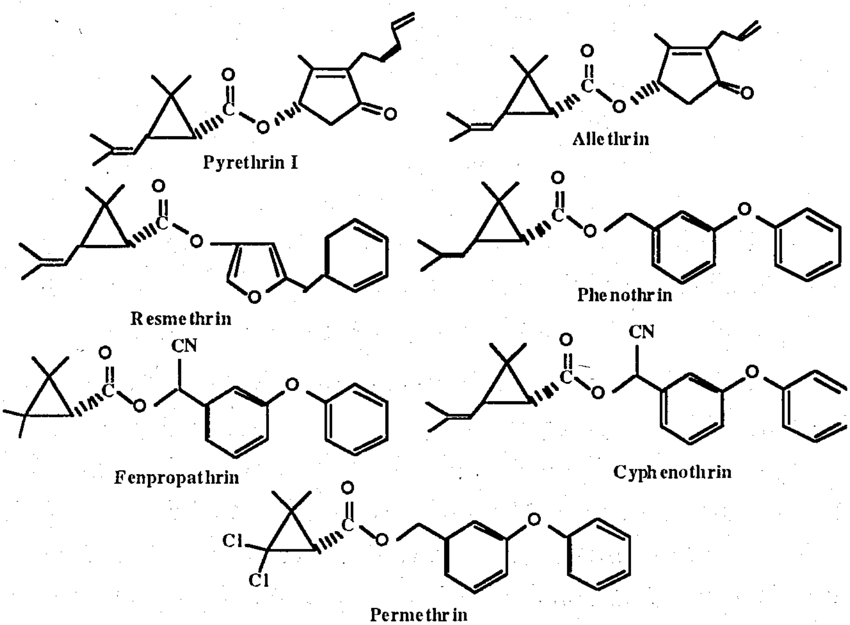
The use of botanical pesticide in fact can be traced back to early Roman times when insecticides were prepared on simple extracts of plants. Until the second world war, pyrethrum, rotenone, nicotine, sabadilla and quassin had been used in the western hemisphere. In the Malay society *Derris eliptica* (tuba), the source of rotenone is used in fish catching. Today, tobacco and derris plant are still used commercially. Nicotine sulfate, marketed under the trade name Black leaf 40 is still effective against aphids and other soft bodied insects[29].



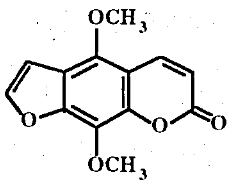
Anabasine Nicotine Nornicotine

Rotenone

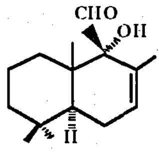
The best-known botanical insecticide is pyrethrum which is extracted from the flowers of *Chrysanthemum cinnerariefolium*. The refined extracts of the toxic components composed of four esters as combination of two different acids and two different alcohols[30]. They are well-known for its fast knock-down effect and still remain important commercially today. Pyrethrin I, which was considered as the most toxic of the four natural esters, has provided the basis of molecular model for vast synthetic studies directed towards the production of compounds more adaptable to crop protection[31]. Such studies have led to the discovery of pyrethroids having increased stability and insecticidal activity such as allethrin, resmethrin, phenothrin, cyphenothrin, fenpropathrin, permethrin, cypermethrin and deltamethrin. Carbamate insecticides have been designed based on the anticholinesterase drug physostigmine. Physostigmine itself was not used as insecticide due to its water solubility and incapability to penetrate insect cuticle. It however serves as the model for carbamate insecticides such as Dimetilan, Carbaryl, Zectran, Propoxur, Mesurol, Carbofuran, Mobam and Temik. Recent advances in the search of botanical insecticides discovered acetogenins as new class of insecticides[32].



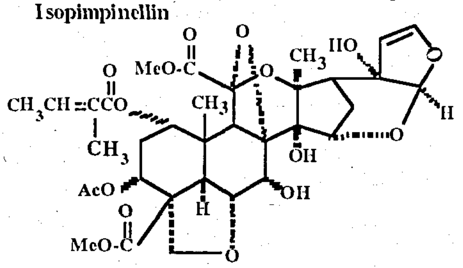
It is generally believed that plants developed its defence mechanisms from predation of other organisms. A tough covering such as bark or cuticle is one way of physical forms of protection. Sticky secretion and development of thorns are ways of repelling predators. The use of toxic secondary metabolites discussed earlier is also a strategy of protection. Other defence mechanisms developed by plants include antifeedants, hormone mimics and anti-hormones. Several antifeedants have been identified from plants but only few showed potential use in plant protection. Warburganal, isopimpinellin and azadirachtin are among the antifeedants isolated from *Warburgia salutaris*, *Oriza japonica* and *Azadirachta indica*, respectively, which have attracted much interest among chemists and entomologists. More interesting development to be seen in practical use of such antifeedants will probably be through genetic manipulation of commercial crops.



Isopimpinellin



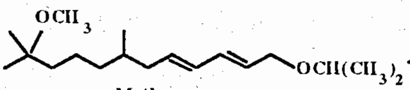
Warbuganal



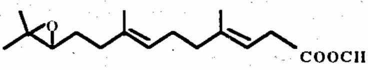
Azadirachtin

Compounds having juvenile hormone activities in regulation of metamorphosis, reproduction, diapause and behaviour have also been discovered from plants. Such compounds include farnesol, juvabione, tagetone, ostruthin, echinolone[23] and juvadecene. Commercial juvenile hormone, Methoprene was developed based on the knowledge of the structure of natural analogue. Yet another interesting discovery in insect control studies is the isolation of simple chromenes, called precocene I and II from *Ageratum houstonianum*. These compounds exhibit anti-juvenile hormone activities by disruption of its production during the insects' growth. Synthesis of their analogues increased their activities significantly.

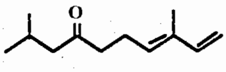
Organisms interact with their environment in many different ways for their survival. Several aspects of plant-insect interaction by means of physical nature and chemical mediation have been acknowledged. Plants utilize bright and distinctly coloured flowers to attract specific insect to assist their pollination while certain plants produce foul smelling flowers for the same purpose. The emission of sesquiterpenes such as *trans*-β-farnesene by plants to repel insect was also recorded[33]. In our laboratory the study on plant-insect interaction between oil palm and its pollinating weevil, *Elaeidobius kamerunicus* revealed the involvement of a single major component of its flower volatiles identified as estragole **(38)**, to attract the insect[34]. The release of the volatile oils by the



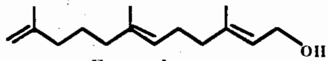
Methoprene



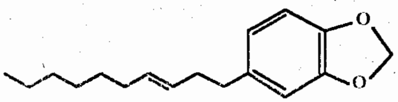
Insect Juvenile Hormone III



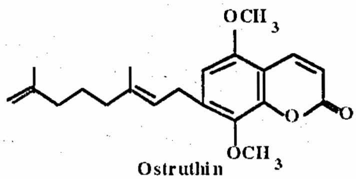
Tagetone



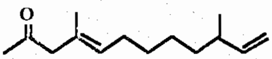
Farnesol



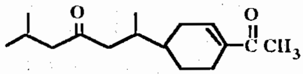
Juvadecene



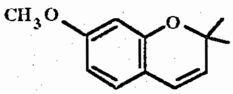
Ostruthin



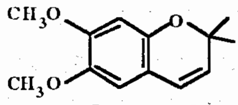
Echinolone



Juvabione

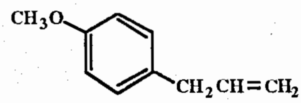


Precocene I



Precocene II

male and female oil palm flowers during anthesis attracts the weevil to lay eggs on the male flowers. Subsequent visit of the weevil to the female flower completes the pollination process of the oil palm. Further study on the structure-activity relationship of estragole analogues in atracting the weevil suggested that the oil palm and *E. kamerunicus* interaction is rather highly specific(35,36,37,38,39). The insect itself is not native to this country. Its introduction to this country in 1981 to take over manual pollination job was launched before any cological impact assessment was carried out. This study, even though does not have a direct economic implication at present time, is relevant in assessing the potential ecological disturbance resulting from its introduction in our ecosystem. In this case we have been fortunate since their interaction with oil palm is highly specific thus possible competition for host with other insects can be excluded.



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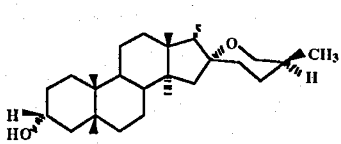
A chemical study on plant - animal interaction has also been carried out in our laboratory with regards to the hepatotoxicity effects of *Brachiaria decumbens* towards sheep[40]. From the rumen extracts of affected sheep we isolated a new sapogenin, *epi*-sarsasapogenin **(39)** along with a known *epi*-smilagenin **(40)**[41].



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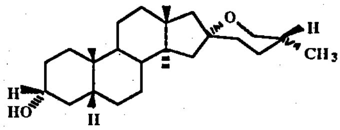


(40)

Our attempt to isolate the corresponding compounds from the grass however was not successful. Later study on the GC-MS analysis of this plant however only managed to identify steroidal sapogenins, diosgenin and yamogenin[42]. We, therefore, concluded that *epi*-sarsasapogenin and *epi*-smilagenin are not present in the grass but rather they may be derived from other sapogenins or saponins of the grass resulting from the microbial or enzymic reaction in the rumen.

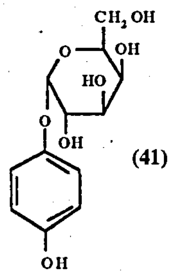
Phytochemicals in Industrialization Program:

Malaysia is endowed with rich and diverse flora and fauna which may contain secondary metabolites having high potential values to people. The genes which determine the biogenetic course of these organisms can even be transferred to other organism to create a desirable quality in the latter or to produce the desired products by modifying the biogenetic pathways of the host organisms. The blend of multiracial society in Malaysia stores a vast knowledge on traditional uses of many of these flora and fauna for health care and other purposes. Even without taking into consideration of the multicultural indigenous people of East Malaysia it was claimed that approximately 15% of the local plants have some medicinal uses to various ethnics[35]. This knowledge can be utilized either solely or in combination with other approaches in the high value natural products discovery programs.

The commercial potential of manufacturing fine chemicals from plants and microorganisms for pharmaceutical, cosmetic, agricultural and other related industries is quite obvious as shown by the success of various multinational organizations capitalizing on this activity. Several multinational pharmaceutical firms have for a long time prospered from producing high-value chemical products from natural sources. Should developing countries like Malaysia also embark into these industries in view of it being capital as well as technology intensive? The answer may not be obvious, and it must be viewed from various perspectives.

In addition to creating new economic resource to the country, utilization of biological resources for the production of high value products will create awareness among the general public on the importance of keeping the natural biological resources for potential future beneficial discoveries. Manufacture of fine chemicals will lay the foundation for other downstream industries including pharmaceuticals, cosmetics, flavours and fragrances, agriculture as well as biotechnology based industries. Existence of fine chemical industries will promote scientific development in the fields such as those related to the above. Furthermore, the knowledge and infrastructure developed in research on natural products such as botany, chemistry and pharmacology are relevant to the development of biotechnology and other newly emerging fields in a country.

Although the benefits from discovery of new natural products are enormous and has always been the primary intention of the research program, the potential discovery and development of known high value products from new sources should not be overlooked. In this respect we are now initiating the development of a plant designated as TTG1 for potential new source of arbutin **(41)**, a commercial product used in cosmetics and as anti-oxidant.



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From a different perspective, research in natural product should not only be narrowly considered as the screening exercise for discovering compounds having potentially high commercial value. It should also be regarded as training ground for the scientists in preparation for their other specific tasks. For example, the training in natural products chemistry is so versatile which include spectroscopy, theoretical organic chemistry, biosynthesis, chromatography and organic synthesis, and require some biochemical or biological uderstanding if the training or research program involves biological systems. Such exposure would enable trainees to adapt themselves to a wide range of research undertakings in industry as well as in various other analytical research including environmental, medical and agricultural areas. These qualified personnel are essential for a country's thrive for industrialisation.

Future Strategies:

The future of our economy is in product manufacturing. Fine chemical industry can be one of the future which can catalyse development of other downstream manufacturing industries in view of the infrastructures developed as a result of the establishment of the former. Currently, the science required for such industries is quite developed even though suffering from inadequate facilities and funds. Research in the chemistry and pharmacology of natural products has been actively pursued in various institutions and other related fields including cell culture, and genetic engineering (related to natural products) should be coming along.

Several aspects of research need to be reinspected and tightened. For example, the current practice of fragmented and isolated works have to be reorganized and coordinated in order to arrive at a more substantial and concrete result at the end of a funding exercise. Specific target(s) of the research program must be identified and adhered to by all participating scientists.

In view of the limited number of qualified scientists in the country, consolidation of expertise and manpower is necessary. Only a limited number of research programs can be effectively handled at a certain time and they must be selected according to necessity as well as appropriateness. The recent setting up of a *National Committee on Natural Products* is a positive move towards this direction.

In view of the potential discovery of new high-value products from our biological resources, an extensive well-coordinated screening program at national level needs to be established. Centers for specific bioactivity screenings and certain sophisticated facilities need to be identified, supported and be able to be shared by all scientists requiring the service. The results of the screenings as well as other follow-up investigations need to be collated and evaluated for proper follow-up actions. Several aspects of research management have been one of the weakness in our current system. Inadequate technician for sophisticated instruments, inconsistent funding system and lack of funds for instrument maintenance have created some discomfort in conducting research. These issues need to be addressed in the next phase of our research undertakings. I am sure the new management team of this university will be able to address these problems.

Although new products discovery will become the major activity, research on commercial development of natural products will also be carried out. Research on alternative approach to production such as through cell culture, genetic manipulation and synthesis are some of the foreseeable activities. Some downstream research, such as products development especially of those primary products that have already been accepted.

Conclusion:

Plants and other living organisms are created for the mankind. Man is the guardian of these resources and it relies upon his ingenuity to maximize the benefits derived from them. This task however requires strong commitment, patience and will-power. In order to be able to fully derive these benefits, one must not only emphasize the immediate returns from utilization of these resource, but one must also view the impacts of their actions in longer term basis. Although the enormous forms of potential economic benefits that can be gained from the utilization of biological resources are quite obvious, living systems need to be understood and even nurtured in order to sustain their contribution to our lives. People need plants and other living organisms to exist. A living organism interacts with its neighbours and distortion in an eco-system can lead to a disastrous consequence to the society. It took millions of years for our mother nature to establish the ecological system we are having now. For our survival and prosperity, we need to learn the intricate interaction system of living things surrounding us in order not to disturb the balance. The information gained can be applied to our benefits.

Conservation of biological diversity has become one of the favourite agenda in many international fora. Eisner wrote "*Species extinction - the death of birth as it has been called- is the silent crisis of our time.*"[43]. Loss of species means permanent loss of chemicals that are potentially unique in nature. It is estimated that , on the basis of past experience such as the NCI screening program, the projected loss of 50,000 species by the end of the century will represent a loss of some 15 billion (1980 USD) to pharmaceutical industry[44]. AIDS and several types of cancer are new in our medical dictionary. There could be other diseases awaiting to be discovered. It is therefore essential that conservation strategies be developed for the future benefit of all mankind.

The potential contribution of natural products researches in our quest to become a developed nation should not be overlooked. Not only that there is great potential of using our biological materials as the sources of new products, the utilization of the genes available in these resources through genetic engineering and cell culture can benefit our agriculture and biotechnology industries. Recently, a number of bioactive compounds have been isolated from plants including one, *Calophyllum lanigerum*, from Malaysia[45]. These discoveries however did not involve any local scientists and therefore the excitement from the discovery and the benefits which may derive from its development were not shared by our people and the country. This represents a loss of national wealth and it should be prevented from happening again.

In our endeavour to discover and develop high value natural products from our biological resources, we have discovered interesting and new knowledge. The experience itself is rewarding enough and allowed us to understand better about other living things around us. It only reaffirms me of how great God is.

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