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Medicinal Plant Research in Malaysia: Scientific Interests and Advances

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ABSTRAK

Kertas kerja ini menggariskan kecenderungan saintifik dan kemajuan dalam penyelidikan tumbuhan ubatan di Malaysia pada lima dekad yang lepas. Pada mulanya minat utama program penyelidikan ialah kajian fitokimia yang membawa kepada penemuan sebatian bioaktif sebagai templet untuk menghasilkan calon dadah baru. Ketika pasaran ubatan herba di Malaysia mengalami pertumbuhan yang luar biasa, pendekatan penyelidikan baru-baru ini telah meliputi aktiviti untuk membangunkan ubatan herba menjadi produk yang berkualiti, berkesan dan selamat untuk penggunaan manusia. Kemajuan dalam teknik-teknik kromatografi dan spektroskopi telah memberi impak yang sangat besar ke atas pengasingan dan elusidasi struktur kandungan tumbuhan ubatan. Pembangunan siri kaedah bioassai dan penggunaan teknik pengasingan berpandukan bioassai telah menyumbang secara signifikan kepada kemajuan penyelidikan tumbatan ubatan di Malaysia. Kajian ke atas beberapa tumbuhan ubatan yang dijalankan oleh saintis tempatan akan diilustrasi sebagai contoh.

Kata kunci: Tumbuhan ubatan, penemuan dadah, ubatan herba, kajian fitokimia, bioassai, teknik kromatografi dan spektrometri.

ABSTRACT

This paper outlines the past five decades of scientific interests and advances in medicinal plant research in Malaysia. Initially the prime interest of research programmes has been on phytochemical studies leading to the discovery of biologically active compounds as chemical templates to produce new drug candidates. As the Malaysian herbal medicine market experiences an extraordinary growth, the research approaches taken have recently included activities to develop herbal medicines into quality, efficacious and safe products for human consumption. Advances in chromatographic and spectroscopic techniques have had a tremendous impact on the isolation and structure elucidation of the constituents of medicinal plants. The development of a series of bioassay methodologies and utilization of bioassay-guided isolation techniques have contributed significantly to the progress of medicinal plant research in Malaysia. Research work on some medicinal plants carried out by the local scientists will be illustrated as examples.

Keywords: Medicinal plants, drug discovery, herbal medicine, phytochemical studies, bioassays, chromatographic and spectroscopic techniques.

INTRODUCTION

Medicinal plants have been used by mankind as a source of medicines since time immemorial. Information on the ancient uses of plant materials as medicines can be found in archeological finds, old literature, history books and pharmacopoeias. In fact in the Quran and the Bible, about 20 and 125 plants are mentioned, respectively, as being used as medicinal agents to treat various ailments (Musselman 1999). More than 35,000 plant species have been reported to be used in various human cultures around the world for medical purposes (Lewington 1993). However, the number could be much higher as knowledge on the indigenous uses of plants was mostly passed on orally from one generation to another and has largely remained undocumented. Burkill (1966), in his extensive compilation of the economic products of the Malay peninsula, recorded not less than 1,300 plants have been used in traditional medicine.

The tropical rain forest plants are biologically and chemically diverse resource as they synthesize various chemicals as defense agents against pests, diseases and predators. They are an excellent reservoir of medicines and chemical leads with which researchers can design and synthesize new drugs. In fact about 25% of the drugs used in modern medicine owe their origins to plants from tropical rainforest (Elliot 1986). The phytochemicals can be used unmodified as drugs, as starting materials for

the partial synthesis of drugs or as molecular models to synthesize new drugs. Of the more than 120 pure pharmaceutical chemicals isolated from about 100 plant species, currently in use as drugs, 40 are obtained from tropical species (Farnsworth & Soejarto 1991). However, fewer than 5% of tropical forest plant species have been examined for chemical compounds and medicinal values (Zakrzewski 2002). The figures are not unusual as systematic drug discovery programmes from plants are largely carried out by multinational drug corporations or research groups of the industrialized countries which possess the technology resources and well-equipped research facilities but have little access to the tropical plant genetic resources. In most tropical countries there is little systematic research effort to screen plants for new drugs as their capacity to productively and sustainably exploit these resources to their full potential is limited; instead commercial activities such as clearing of forests for agricultural purposes and timber extraction predominate and are rapidly destructing the plant genetic resources.

In the past five decades, medicinal plant research in Malaysia has been carried out mainly by researchers from government-funded universities and research institutes with little involvement of industries and multinationals. Although natural products screening programmes are still actively on going in these institutions, there is yet a serious effort to embark on a systematic drug discovery programme at a national level. Most of the work on medicinal plants are inclined towards academic exercises with little emphasis on developmental approach. Some of the promising initial findings have not been used for further research to the eventual development of new drugs. Limitation in funds, facilities, and qualified research personnel and lack of effective research management and collaboration between the research institutions have always been identified as the major stumbling-block to progress in drug research in Malaysia. The great public interest and expansion in the use of herbal medicine have led to new emphasis and drive in medicinal plant research. The research approaches taken have recently included activities to develop herbal medicines into quality, efficacious and safe products for human consumption.

This paper is a review of the past five decades of scientific interests and advances in medicinal plant research in Malaysia. Research work on some medicinal plants carried out by the local scientists will be illustrated as examples.

THE EARLY YEARS – PHYTOCHEMICAL SCREENING ERA

The selection of plant samples for phytochemical screening is generally based on the indigenous uses of plants. In fact the ethnobotanical approach is actually one of several methods that are applied in choosing plants for biological screening in a drug discovery programme. Other plant-collecting methods include the chemotaxonomic approach or the phylogenetic survey where researchers choose close relatives of plants known to produce useful compounds and the ecological survey where selection is based on defensive characteristics of the plants against predators, indicating they produce chemicals capable of exerting an effect on animals. The non-targeted approach i.e. random collection of plant samples is also carried out by researchers especially in areas supporting biological diversity. The gathering of plant samples in Malaysia adopts all the above approaches but the more popular ones are the random and the ethnobotanical methods. In the early years of medicinal plant research, collection of plants from the forests was carried out mainly by natural products chemists from the local universities for the purpose of finding plants for phytochemical screening. It is necessary to record the important contributions of botanists in preparing voucher specimens, classification and identification of plant species for the phytochemical work The voucher specimens are deposited at various herbariums in the local research institutions and universities including the Herbarium of the Forest Research Institute of Malaysia which has been recognized as the country's national herbarium.

The earliest report on medicinal plant research in Malaysia was on the phytochemical screening of 205 plants in Sabah (Authur 1954), followed a few years later by the screening of 200 species in peninsular Malaysia for the presence of alkaloids (Douglas & Kiang 1957). These two publications marked the beginnings of medicinal plant research in Malaysia. Subsequently, more plants were screened chemically for alkaloids, saponins, triterpenes and steroids (Kiang et al. 1961; Chan & Teo 1969, 1972; Carrick et al. 1968; Chan et al. 1977). This simple, cheap, sensitive, selective and rapid chemical tests to determine the presence of certain groups of compounds is an initial step to select plants for further phytochemical studies. In fact phytochemical screening is the earliest step towards the identification of bioactive compounds for the discovery of new drugs. Such work continued to be published until recently by various research groups from the local universities and research institutions (Mohd Ali et al. 1982; Rahmani et al. 1985; Lim et al. 1985; Lajis & Din, 1985; Said et al. 1987;

Kiew et al. 1987; Teo et al. 1990; Jalil et al. 1995; Mohamed et al. 1995; Abu Said et al. 1995; Jusoh et al. 2003).

The strong interest in phytochemical studies by a group of organic chemists from the local universities prompted them to organize annual meetings and workshops to present and discuss research findings in the field of natural products chemistry. The first such meeting was held in 1985 at Universiti Pertanian Malaysia and this was organized co-jointly with the Network for the Chemistry of Biologically Important Natural Products, Australia. The meeting resulted in the publication of the Proceedings of the First Meeting of the Natural Product Research Group which contained articles on phytochemical surveys and ethnobotany (Din et al. 1985). The meetings have since been an annual event not only for phytochemists but also for natural products scientists from other disciplines to interact and create strong working relationship amongst them and also exposed them to the current trend and progress in natural products research. As a results of these meetings The Malaysian Natural Products Society was formed in 1994. UNESCO under its activity, the Regional Network for the Chemistry of Natural Products in South East Asia played important roles in supporting natural products research in Malaysia since the early seventies, especially in providing grants for scientists to organize and participate in regional seminars and conferences. Through this network, Malaysian scientists were able to interact and exchange information with researchers from other countries.

PHYTOCHEMICAL STUDIES – ISOLATION OF COMPOUNDS AND THEIR STRUCTURE ELUCIDATION

The main activities during the early years of medicinal plant research were basic phytochemical studies directed towards isolation of pure new compounds from selected medicinal plants and their structural elucidation. Most phytochemical studies were carried out to isolate alkaloids from families such as Lauraceae, Annonaceae, Rubiaceae and Apocynaceae since alkaloids were generally known to be biologically active and many natural drugs are alkaloids. The researchers anticipated that the isolated compounds would be later assayed for biological activities and be further developed into new pharmaceutical agents. The first report on phytochemical studies of Malaysian plants was on the isolation and structure elucidation of alkaloids of *Uncaria pteropoda*, and later that of *Uncaria gambir*. (Chan et al. 1966, 1968)

A survey of the literature revealed that since the pioneering work of Chan and co-workers in the sixties there was no published work on the isolation and structure elucidation of phytochemicals of Malaysian plants until the early eighties which saw a revival of research. A workshop on the chemistry and structure elucidation of natural products was organized by UNESCO and Universiti Sains Malaysia in 1981. However, the papers presented in the workshop were general discussions on the chemistry of natural products, spectroscopic techniques used for structure elucidation and reviews of work carried out on plants from other countries (Feng et al. 1984). There was a revival of research activity on medicinal plants in the later part of the eighties but at a slow pace. Some notable publications are the indole alkaloids of *Leuconotis* species (Goh et al. 1984, 1986a), the alkaloids of *Uncaria callophylla* (Goh & Ahmad Junan 1985), aporphine alkaloids of *Desmos dasymachalus* (Chan & Toh 1985) and *Pseuduvaria macrophylla* (Hadi et al. 1985), the alkaloids of *Mitragyna speciosa* (Houghton & Said 1986) and goniothalamine oxide of *Goniothalamus macrophyllus* (Sam et al. 1987).

The nineties saw a greater increase in the number of published work and this was in tandem with the small increase in number of people involved in phytochemical work. There were about 50 scientists actively involved in natural products research in the early nineties. Some of these publications could be found in proceedings of national seminars and international conferences held locally (Khozirah et al. 1992; Chan et al. 1993; Said et al. 1996). *Kopsia* species were one of the more popular plants that have been widely investigated by several workers for their alkaloidal contents since the early nineties (Awang et al. 1991; Sevenet et al. 1994; Uzir et al. 1997; Kam et al. 1993, 1994, 1996, 1999a, 1999b; Kam & Choo 2003). Examples of recent publications are on a new dimeric stilbenoid from *Neobalanocarpus heimii* (Weber et al. 2001), coumarins from Malaysian *Micromelum minutum* (Rahmani et al. 2003) and alkaloids from *Tabernaemontana corymbosa* (Kam & Sim 2003) and *Alstonia angustifolia* (Kam & Choo 2004).

The author contributed actively in the phytochemical studies of some Guttiferae species where several compounds were isolated including three new prenylated xanthones, a new neoflavonoid and a new biflavonoid (Goh & Ibrahim 1991; Goh et al. 1992a, 1992b, 1993). He was also involved in the study of aporphine alkaloids of *Aromadendron elegans* (Goh & Ibrahim 1992) and diterpenoids of

Andrographis paniculata (Ibrahim & Waterman 1994). Recent work published in association with the author was the isolation of new indole alkaloids with methyl chanofruticosinate skeletal system from *Kopsia flavida* (Husain et al. 2001). The structures of all the compounds isolated were established on the basis of 2D NMR and other spectroscopic techniques.

Systematic research to determine the chemical composition of new types of essential oils of Malaysian plants began actively in the late eighties by a few groups of local scientists. The work has continued until the present time. The more notable work on essential oils was carried out by scientists from Universiti Kebangsaan Malaysia (Yaakob 1990, Yaakob et al. 1990; Din et al. 1989), Universiti Sains Malaysia (Wong et al. 1992, 1993, 1994) and the Forest Research Institute of Malaysia (Ibrahim 1988; Ibrahim et al.1993, 1994a, 1995, 1996). The most important contributions by the author and co-workers are a series of publications on the essential oils of *Cinnamomum* species (Ibrahim et al. 1990;1992; 1994b, 2002a, 2003, 2004). Prior to these reports on the essential oil constituents, there were earlier reports on the agronomic studies of a number of aromatic plants planted on experimental plots (Anonymous 1969) and on the physical and physico-chemical properties of some popular spices to assess their qualities as compared to the ISO Standards (Mardi Report 1974a, 1974b, 1974c).

ADVANCES IN CHROMATOGRAPHIC AND SPECTROSCOPIC TECHNIQUES

In the early years of phytochemical work, isolation of compounds was carried out manually by the usual chromatographic techniques like open column chromatography, flash chromatography, vacuum liquid chromatography and preparative thin layer chromatography. Subsequent acquisition of newer automated liquid chromatographic techniques such as medium pressure liquid chromatography, reverse phase HPLC, chromatotron and droplet counter current chromatography (DCCC) and the availability of pre-packed columns of various polarity allowed many previously unworkable complex polar mixtures to be successfully fractionated and pure compounds to be isolated in higher yields. The use of capillary columns as alternatives to packed columns in GC together with GC-MS, equipped with extensive collection of library database, resulted in better resolution, faster and easier analysis of complex mixtures of biological origin.

In the early years, structure elucidation posed a big problem to many researchers as the major spectroscopic equipment, i.e. nuclear magnetic resonance (NMR) and mass spectrometer (MS) were not easily available. Many researches had to send samples to institutions of developed countries for these services. The availability of these expensive spectroscopic instrument in many laboratories towards the late nineties facilitated and hastened elucidation of structures. Low fields ^{1}H and ^{13}C NMR (proton noise decoupling, off-resonance technique, DEPT), MS, IR, UV spectra and elemental analysis data were in most cases sufficient to obtain the structures of compounds.

The acquisition of new techniques such as two dimensional high field NMR, liquid chromatography – mass spectrometry (LCMS), chemical ionization and fast atom bombardment mass spectrometry (CI and FAB-MS), Fourier Transform Infra Red spectrophotometry (FTIR) and X-ray crystallography in the early nineties, enabled natural products chemists to confidently characterized and identify structures of large and complicated molecules at submilligram quantities. The acquisition of high field NMR by some laboratories in the mid-nineties to run two-dimensional NMR experiments such as NOESY, HMQC, HMBC and J-modulated has had a tremendous impact on the investigation of the constituents of medicinal plants in Malaysia.

GENERAL SCREENING BIOASSAYS – THE BEGINNING OF A MULTIDISPLINARY APPROACH

Phytochemical work for the sole purpose of studying the chemistry of isolated compounds phased out by the mid-eighties. Most phytochemists had been working in isolation with little interaction with scientists from other disciplines. The approach taken by many research groups gradually shifted from pure phytochemical screening to include biological screening which involved subjecting plant extracts or isolates to various bioassays to determine their biological activities. The phytochemists prepared plant extracts or isolated pure compounds which were then sent to biological scientists for bioactivity studies. This change was the beginning of a multidisciplinary approach in medicinal plant research in Malaysia.

Ironically the first report on biological screening of Malaysian plants was way back in the sixties by a Japanese research group (Nakanishi et al. 1965). Since then there was little report on such publications until the late eighties. The biological screening was limited by the bioassays available and little participation of biological scientists notably pharmacologists in medicinal plant research. Moreover the equipment used in most bioassays was expensive and research grants in this area of research were limited. The earlier assays that were commonly in use were the general screening bioassays which were the simple, cheap and fast *in vitro* bench-top bioassays particularly the brine shrimp lethality, insecticidal tests, antioxidant and antimicrobial assays. Toxicity screening of several plant extracts using the brine shrimp assay by Sam et al. (1988) is one of the more notable work. Other examples of the brine shrimp lethality test on Malaysian plants are by Jalil et al. (1995), Husain et al. (1995) and Mohamed et al. (1995). The insecticidal activities of the extracts of some *Shorea* and Menispermaceae species (Mat Ali et al. 1988; Musa et al. 1988) and the larvicidal activity of some Malaysian plants on three vector mosquitoes (Ibrahim et al. 1996) have been reported. Screening for antimicrobial and antioxidant activities on Zingiberaceae extracts has been carried out (Habsah et al. 2000). The author was also involved in the studies on the toxic and antifungal activities of the essential oils of *Cinnamomum* species (Ibrahim et al. 1994) and the antifungal activity of the essential oils of nine Zingiberaceae species (Ibrahim et al. 2003).

NEW BIOASSAY METHODS

The development and utilization of a series of specialized bioassays in many laboratories in Malaysia commenced in the early nineties. This was largely due to the increase in active participation of biological scientists especially pharmacologists, biochemists and microbiologists and the availability of substantial research grants from the Government through its Intensification of Research in Priority Areas (IRPA) programme which commenced in 1985. Medicinal plant research was given a big boost when development and production of biopharmaceuticals from plants was identified as one of the priority areas. The new bioassay methods include the use of *in vitro* systems such as cultured cells for anticancer, antiviral and antiparasitic assays, *ex vivo* systems involving isolated tissues and organs, *in vivo* systems involving whole animal experiments and the mode of action assays based on specific enzymes or receptors.

Some examples of reports published in the eighties on biological activities of medicinal plants are the *in vitro* antihypertensive activity and cardiovascular effects of alkaloids isolated from several plants notably *Uncaria callophylla* (Goh et al. 1986b; Chang et al. 1989). In the following years the number of papers published on the biological activities of plant extracts and isolates from the local plants increased greatly. Some examples are the anti-tumor promoting activities of Zingiberaceae rhizomes (Vimala et al. 1999), the antimalarial activity of the extracts of *Piper sarmentosum*, *Andrographis paniculata* and *Tinospora crispa* (Nik Rahman et al. 1999), the antimicrobial, antioxidant, antitumour-promoting, cytotoxic and antifungal activities of *Garcinia atroviridis* (Mackeen 2000, 2002).

The mode of action assays were becoming more popular because they were fast, easy to perform, quantitative and could selectively detect biologically active molecules at very low levels. The mode of action assays, employed in high-throughput screening (HTS) techniques, allow a large number of compounds to be screened for a wide range of bioactivities i.e. pharmacological, biochemical, microbiological, toxicological and immunological activities, in a relatively short time. The approach taken by most research groups were to carry out bioactivity studies on crude extracts or isolated pure compounds. This approach has continued over the years and are still widely practiced until today by some research groups. Examples of work carried out based on this approach are the inhibitory effects of xanthones, previously isolated from some Guttiferae species, on platelet-activating factor (PAF) binding to receptor *in vitro* (Ibrahim et al. 2001a), the mechanisms of apoptosis induced by goniothalamin, isolated from *Goniothalamus andersonii*, in the leukemic T-cell line Jurkat and promyelocytic HL-60 leukemia cells (Inayat-Hussain et al. 1999, 2003), the effects of iridiods previously isolated from *Saprosma scortechinii* and *Rothmannia macrophylla* on lipoxygenase and hyaluronidase activities and their activation by beta-glucosidase in the presence of amino acids (Ling et al. 2003).

BIOASSAY-GUIDED ISOLATION TECHNIQUES

Recently, bioassay-guided isolation techniques were gradually adopted by many workers to isolate bioactive compounds. In fact the systematic drug development programmes from natural resources in multinational drug companies are based on the bioassay-guided isolation techniques. Fractionation of active extracts followed by isolation of active compounds are linked with bioassays and most of the time the compounds isolated are responsible for the biological activity of the plant. Bioassay-guided isolation of active compounds involves a strong collaboration between the chemist who is involved in the isolation and the biological scientist who is performing the assay. In some cases both the isolation and bioassay activities are carried out by the same scientist.

The most active compound will be evaluated against the entire spectrum of molecular targets available in the laboratories to determine whether the compound is specific for the desired target. If the compound is found to interact with the entire family of related targets, its potential side effects or toxicity will be determined. However, to date very few publications resulted from the performance of this approach on Malaysian plants. Some examples of bioassay-guided isolation work carried out on Malaysian plants are isolation of reticulatacin, a new bioactive acetogenin from *Annona reticulata* (Saad et al. 1991), antimitotic and cytotoxic flavonols from *Zieridium pseudobtusifolium* and *Acronychia porteri* (Lichius et al. 1994), griffipavixanthone, a novel cytotoxic bixanthone from *Garcinia griffithi* and *G. pavifolia* (Xu et al. 1998), anti-inflammatory agents from *Sandoricum koetjape* (Mat Ali et al. 2004) and a potent PAF antagonist, a new alkenyl resorcinol from *Ardisia elliptica* (Jalil et al. in press).

STRUCTURE-ACTIVITY RELATIONSHIP STUDY

In a structure-activity relationship study (SAR), a specific biological activity of structurally related compounds is evaluated. The most active compound with the least side effects will be selected as a lead structure for further development into a drug candidate. Structure-activity analysis of the tested compounds will determine the molecular structures responsible for the interactions with receptors on target organs. Eventually, the synthetic chemist will attempt to refine the SAR by synthesizing a series of compounds related to the most active structure, to improve the desired activity and to reduce or eliminate the unwanted biological activity. The lead compound in the class will be selected for total synthesis.

SAR study is still at an infancy stage in Malaysia. There is only a few publications on structure-activity analysis of compounds isolated from Malaysian plants. Lack of involvement of synthetic chemists to assist is the main reason for the slow progress in this area of medicinal plant research. The author had been involved in the study on the inhibitory effects of a series of prenylated xanthones on PAF receptor binding *in vitro*. Structure-activity analysis of the compounds revealed that xanthones can represent a new class of natural products which can bind strongly to PAF receptor (Ibrahim et al. 2001a, 2002b). SAR study on inhibition of PAF receptor binding by aporphine alkaloids indicated that the flexibility of the biphenyl system of the aporphine and the presence of methoxy groups at C-9 and C-10 were all preferable in binding to the receptor (Ibrahim et al. 2001b).

TOXICOLOGICAL STUDIES

The most active compound isolated from a plant by the bioassay-guided isolation will be subjected to pharmacological evaluation and a rigorous safety assessment procedures, involving testing against a large variety of different *in vitro* and *in vivo* tests which are designed to reveal different types of toxicity. The toxicity testing include acute toxicity, chronic toxicity, foetal toxicity, effect on fertility, mutagenic and carcinogenic responses. The compound will be tested on cell cultures and isolated tissues to examine any effects on cell reproduction and to identify its carcinogenic potential. Several species of animals are administered with various levels of doses of the compound to check for toxicity over a period of months. If there are significant toxicity in the test animals, even at very high doses of compound, further study on the compound will be discontinued. The activity of structurally related compounds will be similarly evaluated to determine whether the observed toxicity is due to any of the functional groups present in the class of compounds. More analogues of the compound need to be synthesized to finally discover the most promising compound. The compound which pass the toxicity testing is elevated to a drug candidate and is suitable to move on to clinical trials. Example of toxicological studies on Malaysian plants are the teratogenic activity of goniothalamin and

goniothalamin oxide from *Goniothalamus opacus* in mice (Sam et al. 1987), the toxic activities of the essential oils of *Cinnamomum* species (Ibrahim et al. 1994) and the tumour promoting activity of plants used in Malaysian traditional medicine (Ilham et al. 1995).

CLINICAL STUDIES

The most active compound which passed through the safety assessment without any indication of toxicity in the preclinical studies will be subjected to clinical trials. Clinical trials, divided into four difference phases, involve testing the compound on healthy volunteers and patients. To date the only compound from Malaysian plant that has reached this stage of drug development was calanolide A, isolated from *Calophyllum lanigerum* (Soejarto et al. 1991). The compound prevented the HIV-1-induced cytopathic effects in human T-lymphoblastoid cells, especially halted HIV-replication (Kashman et al. 1992). Calanolide A was selected as a drug candidate for early clinical trials in the United States by the National Cancer Institute (NCI) (Soejarto et al. 1995).

RESEARCH COLLABORATION WITH FOREIGN INSTITUTIONS

Like other developing countries, Malaysia is still lacking in the capacity to develop its rich plant genetic resources to their full potential as pharmaceutical agents. Neither is it capable of entering the pharmaceutical market on its own to compete with the multinational drug corporations. The high cost of R & D and limitation in human and technology resources in drug research leave Malaysia with no choice but to collaborate with better equipped international research institutions or pharmaceutical companies.

The publication by Teo et al. (1990) on the phytochemical screening of some plants was the result of one of the earliest research collaboration between a local university with a foreign institution, i.e. University of Malaya and the Institut de Chimie des Substance Naturelles, France which started in 1982. The participation of Japanese scientists in medicinal plant research in Malaysian research institutions and universities was through the Japan International Cooperation Agency (JICA) and the Japanese Society for the Promotion of Science (JSPS) mechanisms which commenced in the late eighties. Malaysian scientists were given the opportunities to visit and participate in short-term research attachments at laboratories in Japan. The involvement of multinationals in biological screening in the late eighties had subjected many Malaysian plants to systematic robotic HTS technology. This technique is based on testing the bioactivity of minute amount of compounds or fractions by means of single-target specific assays using isolated enzymes or receptor binding, or multiple target functional bioassays using test animals, isolated organs or intact cells in a short time. Biotics Limited, a UK-based biotechnology consultancy company, had a screening agreement with the Malaysian Forest Research and Development Board, where the latter supplied plant materials to pharmaceutical companies, Glaxo and SmithKline Beecham, for screening using advanced bioassay technology (Joffe & Thomas 1989). However, there was no significant output published based on this venture.

The NCI started a collaboration with the Sarawak State Government in 1987 to collect plants for anticancer and anti-HIV screening leading to the discovery of novel anti-HIV compounds, calanolide A and calanolide B from *Calophyllum lanigerum* and *C. teysmanii*, respectively (Soejarto et al. 1991). Calanolide A was selected as a drug candidate for early clinical trials in the United States (Saejarto et al. 1995). This major discovery is a milestone in medicinal plant research in Malaysia and an eye-opener on the need to collaborate with established research institutions of developed countries to increase the chances of success in a drug discovery programme. In 2000 the Ministry of Science, Technology and the Environment of Malaysia (MOSTE) supported the Malaysia-MIT Biotechnology Partnership Program (MMBPP), a five-year collaborative effort between Malaysian research institutions and Massachusetts Institute of Technology (MIT), to carry out research which include micropropagation of *Eurycoma longifolia* (Tongkat ali) and chemical fingerprinting of ingredients in formulations of Tongkat ali and enhancement of bioactive metabolite production in *Centella asiatica* by chemical standardization and biological characterization (Anonymous 2004).

HERBAL MEDICINE RESEARCH

The Malaysian herbal product market is experiencing a tremendous growth. Malaysia consumes RM 1.2 billion worth of imported herbal products annually (Mohd Nor 1998). More people are turning to herbal products as alternative to the conventional therapeutic medicine or as nutritional and dietary supplements. There is an increased trend of incorporating herbal therapy into modern medical practice by many mainstream healthcare professionals. Many of the herbal preparations claim to offer relief and prevention of adverse health conditions. However, most of them are not satisfactorily provided with information on their ingredients, indications, dosage, pharmacology, contraindications and possible adverse health effects associated with prolonged use. There is concern for the lack of standardization of herbal preparations to guarantee their safety, quality and efficacy. Thus, there is an urgent need to conduct scientific research to provide experimental evidence of safety, efficacy and quality of herbal medicines while also investigating the plants as sources for new lead structures for drug development.

In response to the increased use of medicinal plants by the Malaysian population, the government in its 7th Malaysian Plan had identified several strategies to enhance the development of the local herbal industry. In 1995, FRIM was given the mandate to set up a National Committee on Medicinal Plants (NCMP) which was comprised of representatives from the universities, research institutions, government agencies and the local herbal industry. One of the major outputs of this collaborative effort was the publication of the monograph on 20 selected medicinal plants (Zhari et al. 1999). However, due to lukewarm support from participating parties, there has not been much progress in the implementation of the proposed master plan for R & D in herbal medicine research. The approval by the government of the establishment of the National Committee for Research & Development in Herbal Medicine (NRDHM) in 2002 led to the revival of the NCMP's activities. To date the committee has managed to come up with guidelines for levels and kinds of evidence to support claims, standardization, safety and clinical evaluations and intellectual property rights management. The five-year collaborative effort supported by MOSTE between Malaysian research institutions and MIT under the MMBPP, as mentioned earlier, contributed towards human resource development and training in herbal medicine research. The collaboration has recently resulted in the publication on genetic diversity of *E. longifolia* inferred from single nucleotide polymorphisms (Osman et al. 2003).

In the 8th Malaysia plan, the government had allocated research funds under the IRPA mechanisms to embark on research programmes to put some of the more widely used medicinal plants such as *Andrographis paniculata* (Hempedu bumi), *Labisia pumila* (Kacip fatimah), *Orthosiphon speciosa* (Misai kucing), *Morinda citrifolia* (Mengkudu) and selected Zingiberaceae species under close scientific and clinical scrutiny. At present, five research groups comprising scientists from various academic and research institutions are actively involved in all aspects of herbal research on the above-mentioned medicinal plants as follows: effective processing of medicinal plants for optimum production of herbal extracts; qualitative and quantitative analyses of herbal extracts for standardization and quality control purposes; pharmacognostic studies to develop monographs of medicinal plants for standard reference; *in vitro* and *in vivo* studies to determine biochemical, immunological, toxicological and pharmacological effects of herbal extracts; toxicological studies of herbal preparations; pharmacokinetic studies of herbal preparations; development of herbal medicines into modern pharmaceutical forms; clinical trials on standardized herbal preparations for various medical indications.

CONCLUSIONS

Despite the scientific interests and advances in the past five decades of medicinal plant research in Malaysia, to date efforts to discover new bioactive agents from the flora for use as chemical leads in the development of new drugs have not experienced much success. The scientific values of most local herbal preparations in terms of quality, safety and efficacy have yet to be established. There is a need to strategize research approach at the national level which should be based on the integration of human and technology resources available and the establishment of smart partnership between academic and research institutions, industries and multinational drug corporations. We have to learn from the experiences of the already successful research collaborations to increase the chances of success to discover new drugs from the Malaysian tropical rainforest. Unless the right research strategy is pursued, it will take more than a few more decades for Malaysia to establish its research and drug design capacity and be a serious competitor in the pharmaceutical and herbal markets. We have to keep abreast with new technologies which are already playing more important roles in medicinal plant research such as the advances in screening methodologies, the development of molecular biology and

biotechnology and the use of computer technology in rational drug design. The role of combinatorial chemistry in drug discovery and the future impact of genomics, proteomics and metabolomics in medicinal plant research should also be given due consideration.

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