# Malay traditional medicine

## An overview of scientific and technological progress

**Jamia Azdina Jamal**

**This article describes the principal practices and status of scientific research and development (R&D) of Malay traditional medicine. An example of a systematic scientific study on *Labisia pumila* var. *alata* illustrates how a traditional preparation has been transformed through research into a modern pharmaceutical dosage form. Several business opportunities and strategies are suggested for small and medium scale enterprises (SMEs) that are interested in traditional medicinal products, particularly herbal products. The article concludes that industry must use a holistic approach to comply with consumer expectations of herbal products.**

**Dr. (Ms.) Jamia Azdina Jamal**
*Department of Pharmacy*
*Faculty of Allied Health Sciences*
*National University of Malaysia*
*Jalan Raja Muda Abdul Aziz*
*53100 Kuala Lumpur, Malaysia*
*Tel: (+60-3) 4040 5303*
*Fax: (+60-3) 2698 3271*
*E-mail: jamia@medic.ukm.my*

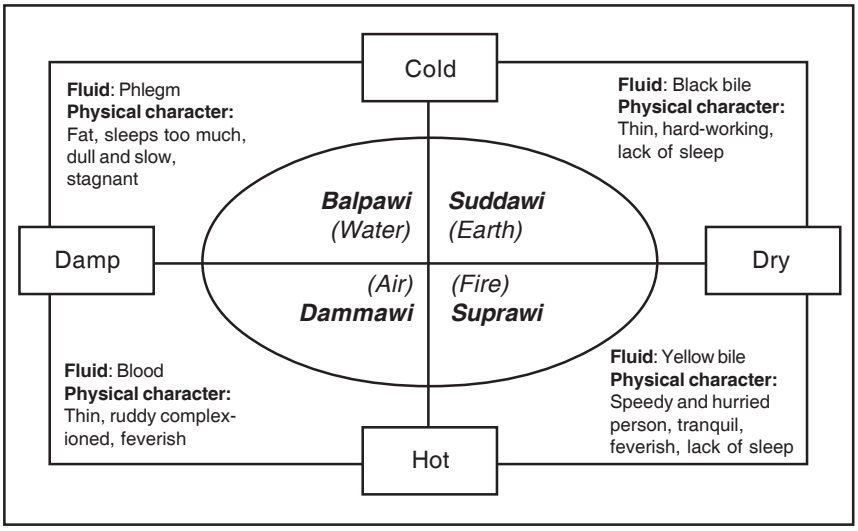
## Introduction

The World Health Organization (WHO) defines traditional medicine (TM) as "health practices, approaches, knowledge and beliefs incorporating plant, animal and mineral-based medicines, spiritual therapies, manual techniques and exercises, applied singularly or in combination, to treat, diagnose and prevent illnesses or maintain well-being" (WHO, 2003a).

The popularity of, and demand for, medicinal plants as health supplements or for medicinal purposes have been increasing worldwide. The renewed interest of knowledgeable consumers could be associated with increasing information and availability of herbal supplements globally. The demand can be demonstrated statistically. In 1999 alone, sales of herbal products worldwide had aggregated to US$ 80 billion. In the same year, the Malaysian market for natural or herbal products, medicinal plants and aromatic plants including aquatic animals was estimated at RM 4.6 billion with an annual growth projection of 15-20 per cent.

Malaysia has great potential to develop her abundant natural resources to increase the market based on herbal products. This is evident from a 1935 report[1] that in peninsular Malaysia alone there are about 550 genera of tropical plants, containing over 1,300 species possessing medicinal values. Of these, several are medicinal plants yielding clinically useful drugs, some of which are listed in Table 1. However, these plants have not been extensively cultivated or exploited here. Some examples of popular Malaysian plants

**Figure 1: Principles of the Malay traditional medicine based on the Greek model of elements and humours**




currently undergoing extensive research are the male aphrodisiac *Eurycoma longifolia* Jack. (*tongkat ali*), *Labisia pumila* (*kacip fatimah*), *Andrographis paniculata* (*hempedu bumi*), *Orthosiphon stamineus* (*misai kucing*), *Centella asiatica* (*pegaga*), *Phyllanthus niruri* (*dukung anak*), *Momordica charantia* (*peria*) and others.

This article briefly describes the practice of traditional medicine by the Malay community, which comprises the majority of the Malaysian population, and the application of science and technology in transforming traditional preparations into modern pharmaceutical dosage forms. It also includes a scientific study on a Malay traditional medicine, *Labisia pumila* var. *alata*. It covers the standardization of herbal products to provide information and understanding of the requirement and significance of the principal elements. It also makes several suggestions, based on learning experiences, for local and international small and medium scale enterprises (SMEs) that are interested in the industry of traditional medicinal products, particularly herbal products.

## History

The principles of Malay traditional medicine are generally based on the Arabic *Unani* medicine and Galenic philosophy. However, it is also influenced by other practices of Indonesian, Chinese, Indian and *orang asli* (indigenous people) traditional medicines.[2] The treatment of ailments uses a holistic approach, involving physical, spiritual, mental, emotional and behavioural factors. Often the diagnosis of a particular disease is made based on an examination of physical conditions and a determination of spiritual influences such as "bad spirits" and ghosts.

In Malay traditional medicine, the physical characteristics of a person are believed to be constituted of four elements - *suprawi* (fire), *suddawi* (earth), *dammawi* (wind) and *balpawi* (water) (Figure 1).[2, 3] These elements, humours and descriptions of ailments are similar to those described by the Greek model of elements and humours.

Besides chants (*jampi*), prayers (*doa*), massage, abstinence (*pantang*) and other practices, the Malay traditional medicine also utilizes various natural resources from plants, animals, microorganisms and minerals for the purpose of treating and preventing illnesses, and for rehabilitation and health promotion. Medications containing single or compound medicinal plants may be dispensed in many forms, such as powders, capsules, pills, *makjun*, medicated oils, simple distillates, decoctions, infusions, paste and poultices.

## Scientific research

Documentation of Malay TM practices is rather scarce. Most practices rely on old references, such as *Mujarabat Melayu*, *Tajul Muluk*, *Tajus as Salatin* and *Surat Tib Ubat*. The earliest scripts on the ethno-botanical uses of Malaysian plants dated back to the time of British colonialism. Some of these were publications[4, 5, 6, 7, 1, 8] providing monumental references for researchers on the utilization of medicinal plants in Malay traditional medicine.

Laboratory-based scientific research of Malaysian medicinal plants commenced with phytochemical screening.[9, 10, 11, 12] This was followed by the isolation and structural elucidation of pure compounds work in the sixties.[13] Since then research has greatly expanded on various medicinal plants, employing diverse research methodologies, by several groups of researchers, either locally or internationally.[14]

Due to a global awareness of the importance of medicinal plants, research and development (R&D) on Malaysian herbals has become of prime interest in most universities and research institutions. The Malaysian government has given substantial support and, since 1985, specific research funding had been allocated through its Intensified Research in Priority Areas (IRPA) programme. Current R&D on Malay traditional medicine is concentrated on ailment-based medicinal plants, using techniques such as bioassay-guided isolation, determination of biological, pharmacological and toxicological effects, and herbal product development; and clinical trials.

## Registration and quality control of TM products

WHO defines herbal medicines as "finished, labelled medicinal products that contain as active ingredients aerial or underground parts of plants, or other plant material, or combinations thereof, whether in the crude state or as plant preparations. Plant material includes juices, gums, fatty oils, essential oils, and any other substances of this nature. Herbal medicines may contain excipients in addition to the active ingredients. Medicines containing plant material combined with chemically defined substances, including chemically defined, isolated constituents of plants, are not considered to be herbal

**Table 1: Some Malaysian plants yielding clinically useful drugs[a]**

| Species (Family) | Local Malay name | Drug | Action/ Clinical use |
|---|---|---|---|
| *Ananas comosus* (L.) Merr. (Bromeliaceae) | Nenas | Bromelain | Anti-inflammatory, proteolytic agent |
| *Andrographis paniculata* Nees (Acanthaceae) | Pokok cerita, hempedu bumi | Andrographolide, neoandrographolide | Bacillary dysentery |
| *Ardisia japonica* Bl. (Myrsinaceae) | - | Bergenin | Anti-tussive |
| *Areca catechu* L. (Palmae) | Pokok pinang | Arecoline | Anthelmintic |
| *Azadirachta indica* Juss. (Meliaceae) | Pokok mambu | Azadirachtin | Insecticide (on non-food plants) |
| *Carica papaya* L. (Caricaceae) | Betik | Chymopapain | Proteolytic, mucolytic |
| *Cassia* app. (Leguminosae) | - | Anthraquinones | Laxative |
| *Catharanthus roseus* (L.) G. Don (Apocynaceae) | Kemunting cina | Vinblastine, vincristine | Anti-tumour |
| *Centella asiatica* (L.) Urban (Umbelliferae) | Pegaga | Asiaticoside | Vulnerary |
| *Cinchona ledgeriana* Moens ex Trimen (Rubiaceae) | Kuinin | Quinidine Quinine | Anti-arrythmic, Anti-malarial, anti-pyretic |
| *Curcuma longa* L. (Zingiberaceae) | Kunyit | Curcumin | Choleretic |
| *Datura metel* L. (Solanaceae) | Kecubung | Scopolamine | Sedative |
| *Dioscorea* spp. (Dioscoreaceae) | Gadung | Diosgenin | Contraceptive |
| *Glycyrrhiza glabra* L. (Leguminosae) | Kayu manis cina | Glycyrrhizin | Anti-inflammatory, sweetener |
| *Gossypium* spp. (Malvaceae) | Pokok kapas | Gossypol | Male contraceptive |
| *Mentha* spp. (Juncaceae) | Pudina | Menthol | Rubefacient |
| *Nicotiana tabacum* L. (Solanaceae) | Tembakau | Nicotine | Insecticide |
| *Quisqualis indica* L. (Combretaceae) | Akar dani, akar pontianak | Quisqualic acid | Anthelmintic |
| *Rauwolfia serpentina* (L.) Benth. Ex Kurz (Apocynaceae) | - | Ajmalicine Rescinnamine | Circulatory disorders, Anti-hypertensive, tranquillizer |
| *Ricinus communis* L. (Euphorbiaceae) | Jarak | Castor oil | Laxative |
| *Strophantus pratus* Baill. (Apocynaceae) | - | Ouabain | Cardiotonic |
| *Strychnos nux-vomica* L. (Loganiaceae) | - | Strychnine | CNS stimulant |

[a] Based on data from Farnsworth & Soejarto (1992)[36] and Burkill (1935)[1]

medicines. Exceptionally, in some countries, herbal medicines may also contain, by tradition, natural organic or inorganic active ingredients which are not of plant origin" (WHO, 1996a).

In the wake of increasing availability of herbal products and their usage by consumers, the Malaysian government imposed the Control of Drugs and Cosmetics Regulation 1984 in the year 1992, whereby all herbal products intended to be produced, imported and sold for human consumption must be registered with the Malaysian Ministry of Health in order to ensure and control the quality, safety and efficacy of the herbal products.[15] This step marked the beginning of a systematic regulatory control over herbal products prepared and sold in pharmaceutical dosage forms, such as capsules, tablets, pills, liquid preparations, creams, lotions, suppositories, patches and others. Currently every registered traditional medicinal product bears the registration number on its label or package, starting with PBKD or MAL and ending with T which denotes it is a traditional medicine product.

All manufacturers, importers, suppliers and wholesalers are also required to be licensed by the Drug Control Authority (DCA) of the Malaysian Ministry of Health. By the end of 2003, a total of 138 manufacturers and 121 importers of traditional medicines had

registered with the DCA. Manufacturers must be in full compliance with the Code of Good Manufacturing Practice, which is currently based on the WHO Code. Every product submitted for registration is subject to laboratory analysis of physical, chemical and biological screening and testing. By law, only registered herbal products are allowed to enter the Malaysian market and these are also subject to regular and random post-marketing surveillance and testing. However, the present analytical procedures are rather restricted and minimal, focusing only on several tests for quality and safety:

- Dosage performance: (i) uniformity of weight and (ii) disintegration test (for tablets, pills and capsules); and
- Safety assessment: tests for (i) heavy metals (arsenic, mercury, lead and cadmium), (ii) aerobic microbial content (gram positive and gram negative bacteria, enterobacteria, *Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus, Salmonella* and fungi) and (iii) scheduled poisons, such as agents for sexual dysfunction (sildenafil and taladafil), slimming agents (sibutramine, fenfluramine and phentramine), antihistamine/antitussive (chlorpheniramine, promethazine, etc), whitening agent (hydroquinone and tretinoin) and steroids (dexamethasone, betamethasone, etc).

Due to limited information on pharmacognostical data, biological activity, active ingredient(s), marker compounds and toxicity effects of many Malaysian medicinal plants utilized in various herbal products, the regulatory body is unable to screen for the identity of ingredients as indicated on the product label, to determine the content of potentially toxic substances and to assay the content of active ingredient(s) or marker compounds which are responsible for the specified activity. Thus Ibrahim[16] suggested that more stringent quality control procedures be implemented in order to curb unscrupulous vendors from marketing unsubstantiated or falsely claimed quality, safety and effectiveness in herbal products.

In Malaysia, herbal medicines are also subject to other related regulatory acts, such as the Medicines Act (Advertisement & Sales) 1956 (Revised 1983); the Poisons Act 1952 (Revised 1989); the Drug Sales Act 1952 (Revised 1989); and the Wild Species Act 1972. The DCA of Malaysia prohibits all TM products from making any therapeutic claims of the cure, treatment, and prevention of certain diseases, 20 of which are listed in Table 2.

However, some unethical traders have used other terminologies or wordings bearing similar indications, or have distributed pamphlets stating the prohibited indications in order to promote sales. On the other hand, functional claims, such as increased strength and vitality, are permitted. Therapeutic claims may be allowed for properly standardized herbal products with proven safety and efficacy, supported by sound clinical data.

## Herbal monographs

Herbal monographs in national pharmacopoeias and other authoritative documents play an important role in the authentication of herbal materials.

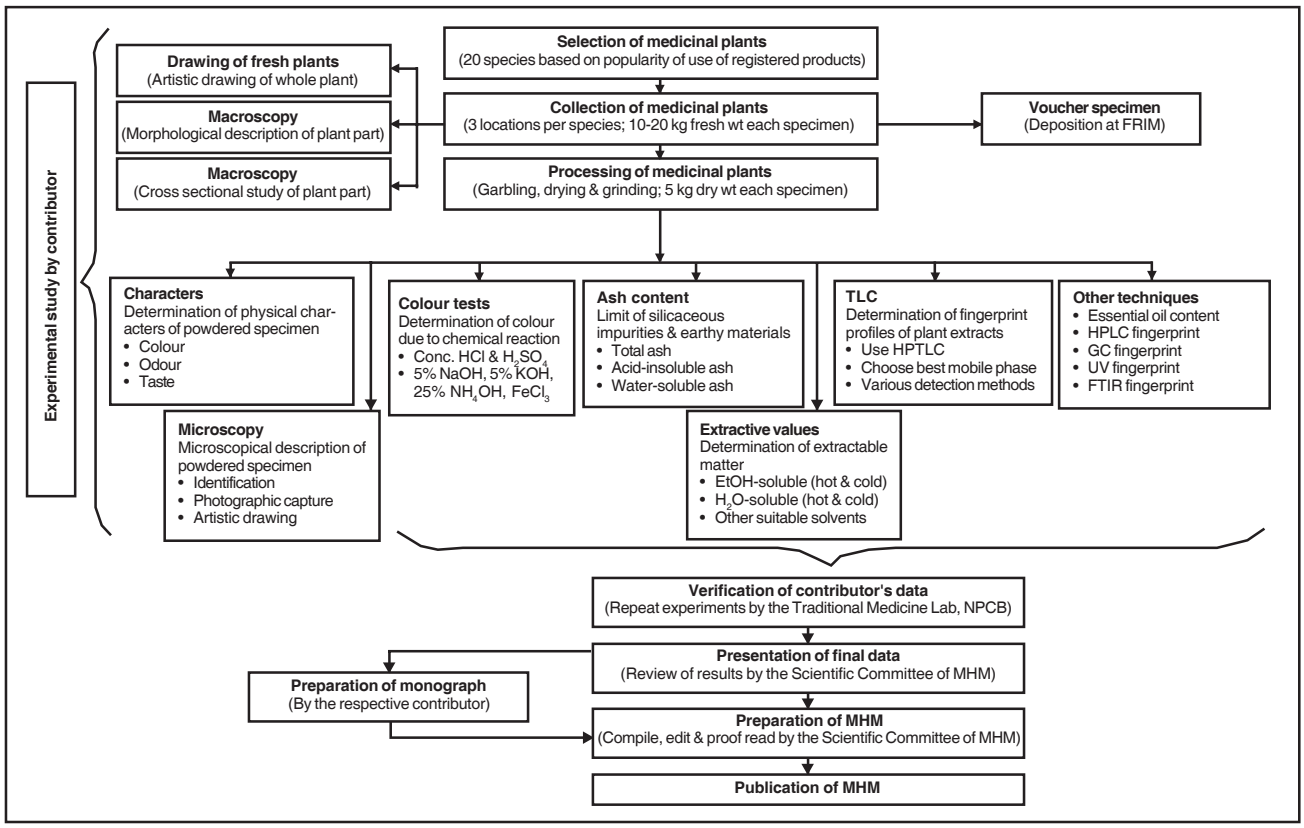
A monograph in this context is a written specification that describes the principal features of a botanical drug and provides information and ways in which these features can be determined that allows for its proper identification and quality standardization for "fitness of use".

A pharmacopoeia, on the other hand, consists of a collection of several monographs. Such standard specifications are actually the key documents in a quality assurance process for the production of well-defined quality, safety and efficacy of herbal drugs and preparations.

In many parts of the world, herbal drugs (herbal raw materials) are required to be authenticated to the relevant monograph in national pharmacopoeias such as British Pharmacopoeia (BP), European Pharmacopoeia (EP) (BP-EP has 184 herbal drugs and preparations), the United States Pharmacopoeia and National Formulary (USP-NF) (28 herbal drugs), the Pharmacopoeia of the People's Republic of China (992 *materia medica* and medicines), the Ayurvedic Pharmacopoeia of India (API) (362 herbal drugs and preparations) and others, if such monographs exist. Examples of the monographs included in the BP-EP are Alexandrian senna (*Cassia senna*), aloe (*Aloe spp.*), belladonna (*Atropa belladonna*), centella (*Centella asiatica*), cinnamon bark (*Cinnamomum zeylanicum*), feverfew (*Tanacetum parthenium*), ginkgo (*Gingko biloba*), ginger (*Zingiber officinale*), ginseng (*Panax ginseng*), isphagula (*Plantago ovata*), Java tea *(Orthosiphon aristatus*), Java tumeric (*Curcuma domestica*), lavender (*Lavandula angustifolia*), roselle (*Hibiscus sabdariffa*), etc. Other official documents of herbal pharmacopoeias are British Herbal Pharmacopoeia (233 medicinal plants), The American Herbal Pharmacopoeia (19 medicinal plants), Complete German Commission E Monographs (107 medicinal plants), ESCOP Monographs (60 medicinal plants), and WHO Monographs of Selected Medicinal Plants (92 medicinal plants). These would include monographs for Aetheroleum Melaleucae Alternifoliae (*Melaleuca alternifolia*), Black Cohosh (*Actaea racemosa),* Dang Gui Root (*Angelica sinensis*), Herba Andrographidis (*Andrographis paniculata*), Herba Centellae (*Centella asiatica*), Echinaceae (*Echinacea spp*), Reishi mushroom (*Ganoderma lucidum*), Valerian Root (*Valeriana officinalis*), etc.

In Malaysia a herbal drug that is the raw material used for the manufacturing of pharmaceuticals from a vegetable source and intended for therapeutic purposes, is authenticated and tested to a relevant monograph available from any official pharmacopoeias or documents. However, to date, preparation and registration of herbal products for supplementation purposes often do not require rigorous physicochemical tests for the raw materials. Standardization of a raw material would mean authenticating and controlling the quality of the plant material used for product manufacturing; that is, it should have an acceptable content of bioactive components; and it should be safe from toxic impurities (e.g. adulteration of poisonous plant materials, deteriorated toxic phytochemicals, heavy metals and microbial contamination). Passing such physicochemical, and sometimes biological tests, of a mono-

**Figure 2: Flow chart of research methodology performed for every volume of Malaysian Herbal Monograph (MHM)**
(Each contributor is responsible for generating the quality control data of the selected medicinal plant; the data is then verified by the Traditional Medicine Laboratory of National Pharmaceutical Control Bureau (NPCB) of the Ministry of Health, Malaysia.)




graph would be a guarantee that the raw material is of pharmacopoeial quality and thus qualifies to be used for the production of a standardized herbal product with consistent efficacy and safety.

Although monographs of commonly used medicinal plants are already available internationally, a monograph of a Malaysian medicinal plant has to be developed in order to suit local species, and geographical and environmental conditions. That is also why many countries develop their own herbal pharmacopoeias; like the Japanese Standards for Herbal Medicines (248 medicinal plants), the Indian Herbal Pharmacopoeia (52 medicinal plants), *Materia Medika Indonesia,* The Philippine National Formulary, Medicinal Plants of Thailand and the Standard of Asean Herbal Medicine.

Thus, the Scientific Committee of Malaysian Herbal Monographs (SCMHM) believes that the work on developing monographs for Malaysian medicinal plants is relevant in order to provide a quality standard for manufacturing of local herbals, as well as to be in line with the neighbouring countries in terms of controlling quality of herbal products.

The first volume of the Malaysian Herbal Monograph (MHM)[17] was published in 1999, containing 20 monographs of selected Malaysian medicinal plants. Work is under way to publish subsequent volumes of the MHM, with 20 Malaysian medicinal plants per volume. A summary of the standard protocol for the development of MHM is shown in Figure 2, involving multidisciplinary scientists from various universities and research institutions. The monographs can then be utilized by the manufacturers of Malaysian herbal products and regulatory authorities as the principal quality control documents. It is hoped that the government and herbal industries continue to support the monograph research to achieve holistic benefits.

## Phytopharmaceutical technology

In most TM practices, a patient is prescribed with a tailor-made remedy by a qualified and properly trained traditional practitioner. The remedies are mostly prepared in the form of liquid (e.g. juice, decoction, infusion, tincture, etc.), solid (e.g. dry powder, dry exudate), paste and oil. Treatment is often limited to the period when the person is having the ailment. Currently many traditionally prepared remedies have been transformed into modern pharmaceutical dosage forms for product reputation, convenience of the consumers and potential sales.

Ironically, these herbal medicines have been considered as general health supplements that consumers take every day for an unlimited period. But unregulated or inappropriate use of herbal medicines can have negative or dangerous effects. For example, the traditional Chinese medicine ephe-

**Table 2: List of therapeutic claims for TM products that are prohibited by the Drug Control Agency of Malaysia**

| | |
|---|---|
| 1. Diseases or defects of the kidney | 12. Hernia or rupture |
| 2. Diseases or defects of the heart | 13. Diseases of the eye |
| 3. Diabetes | 14. Hypertension |
| 4. Epilepsy | 15. Mental disorder |
| 5. Paralysis | 16. Infertility |
| 6. Tuberculosis | 17. Frigidity |
| 7. Asthma | 18. Impairment of the sexual function or impotency |
| 8. Leprosy | 19. Venereal disease |
| 9. Cancer | 20. Nervous debility, or other complaint or infirmity, arising from or relating to sexual intercourse |
| 10. Deafness | |
| 11. Drug addiction | |

dra, for treating respiratory congestion, was used in the USA as a dietary aid, whose over-dosage led to deaths, heart attacks and strokes (WHO, 2003a).

One must bear in mind that plants contain numerous chemicals as a result of their natural metabolic activities. These chemicals may be essential for plant growth or as by-products of its metabolism; they may also be potentially useful as food or medicine, or potentially harmful or poisonous for people and animals. For example, starch functions as an energy store for some plants, has nutritional value for humans and is utilized as a pharmaceutical excipient. Morphine is obtained from the opium poppy (*Papaver somniferum*) as a powerful analgesic, anti-tussive and anti-diarrhoeal, but can also have toxic effects, including impairment of mental performance, euphoria, drowsiness, lethargy, blurred vision and constipation. In fact, some plants can cause allergic reactions, such as irritation to the respiratory system, skin, eyes and oral cavity. Thus, all medicinal plant materials, utilized either internally or externally, have to be considered as medicines. Strict control and careful administration of herbal products are vital to provide consumers with standardized quality, safety and efficacy.

Standardization procedures for herbal medicines should not be limited to finished products only. They should take a holistic approach, covering at least the following areas:

- Selection of a "gold" breed of medicinal plant;
- Cultivation techniques and essential growth requirements (e.g. geographical and climatic conditions);
- Harvesting period (e.g. age of plant), time (e.g. day or night, season, etc) and methods (e.g. manual or mechanical);
- Treatment processes (e.g. garbling, drying, grinding, extraction, etc);
- Quality control of plant materials (e.g. macroscopy and microscopy; identification tests using chromatographic and spectroscopic analysis; gravimetric analysis of extractable matter; limit tests for moisture, ash, heavy metals, microbial and pesticide contamination; assay of bioactive or chemical markers);
- Manufacturing of herbal products (e.g. herbal tea in sachets, pharmaceutical dosage forms, etc.);
- Packaging materials (e.g. plastic or glass bottles, blister pack, etc.);
- Sterilization techniques;
- Storage conditions (e.g. temperature, shelf life); and
- Transportation methods.

These activities would involve multidisciplinary experts, such as botanists, farmers, phytochemists, biochemists, pharmacologists, pharmaceutical analysts, biotechnologists, and chemical engineers.

Standardization of herbal medicines is of utmost importance in order to ensure consistent batch-to-batch quality, safety and efficacy. The efficacy and safety aspects of a medicinal plant are due to its biological activity, which, in turn, is based mainly on the amount or concentration of the chemicals present in raw or processed (e.g. extract, distillate, oil, juice) forms. Because these chemicals are metabolic products of plants, their formation and stability are often affected by various internal and external factors - genes, geography (e.g. altitude, latitude and soil type), climate (e.g. sunlight, humidity and rainfall) and deterioration (fungal and bacterial attack, temperature, hydrolysis by moisture, photodecomposition by direct exposure to sunlight, oxidation by oxygen, etc).

The WHO has published several important guidelines pertaining to various aspects of herbal medicines, such as the regulation and practice of herbal medicines (WHO/TRM, 1998; WHO/WPRO, 1998), assessment of safety and efficacy (WHO/WPRO, 1993; WHO, 1996a; WHO MD, 2000; WHO, 2004), quality control of medicinal plant materials (WHO, 1998a), agricultural and collection practices (WHO, 2003b), manufacturing processes (WHO, 1996b), evaluation of medicinal dosage forms (WHO, 1998b) and conservation (WHO, 1993). These cover the whole spectrum of standardization procedures of herbal medicines. An outline of essential standardization processes is shown in Figure 3.

Proper quality control can ensure consumer and operator safety, consistent formulation and therapeutic dose of medicines, reliable clinical effect, brand reputation and cost effectiveness; besides being a requirement of quality assurance in Good Manufacturing Practice (GMP).

## Case study: *Labisia pumila*

*Labisia pumila* (Bl.) F.-Vill (syn.: *Labisia pothoina* Lindl., family: *Myrsinaceae*), popularly known as *Kacip Fatimah*, has been used by many generations of Malay women to induce and facilitate childbirth, and as a post-partum medicine,[18] as well as for flatulence, dysentery, dysmenorrhoea and gonorrhoea, 'sickness in the bones'[1] and haemorrhoids.[19]

There are three varieties of *L. pumila*, i.e. *L. pumila* var. *pumila*, *L. pumila* var.

*alata* (Scheff.) Mez. and *L. pumila* var. *lanceolata* (Scheff.) Mez.[20] Preliminary screening of the medicinal plants suggests that the var. *alata* is more commonly used in traditional medicine preparations.

Previous scientific studies revealed that extracts of *L. pumila* had various activities such as antibacterial effect[21], oestrogenicity *in vitro*,[22, 23] PAF receptor binding inhibition *in vitro*[24] and anti-oedema *in vivo*.[25] The plant was also found to contain benzoquinoid derivative (Houghton & Jamal, 1999),[26] alkenyl resorcinols[27] and triterpenoid compound (unpublished data).

Based on various sources of ethnobotanical information,[1, 28, 21, 29] it can be assumed that *L. pumila* has traditionally been prepared in a form of water decoction of either the leaf part or the root part or the whole plant. The preparation may also contain other medicinal plants.

Recently a supplement drink containing *L. pumila* var. *alata* was introduced into the Malaysian market and is becoming popular. Thus this laboratory-based study is aimed to formulate the water extract of *L. pumila* var. *alata* into a solid pharmaceutical dosage form of tablets for the convenience of administration by consumers. Various research methodologies and data, such as quality control of raw materials based on pharmacognostical evaluation, extraction techniques and parameters, and tablet formulations, have been obtained for the purpose of proper standardization to help ensure the quality, safety and efficacy of herbal products containing *L. pumila* var. *alata*.

## Quality control of raw materials

The flow of quality control processes of *L. pumila* var. *alata* is summarized in Figure 4. Based on the information obtained from the study, *L. pumila* var. *alata* can be physically differentiated from other varieties based on the broadly-winged character of the leaf petiole (Figure 5). A powder of the dried *L. pumila* var. *alata* would contain characteristic multicellular peltate trichome and numerous calcium oxalate clyster crystals (Figure 6) when analyzed microscopically.

**Figure 3: Flow of research methodology for the standardization of herbal medicinal products**

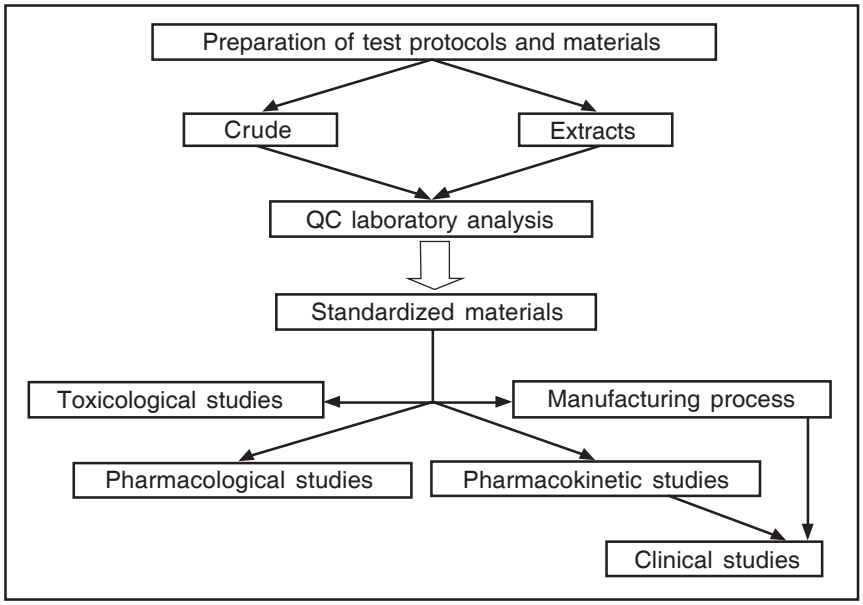
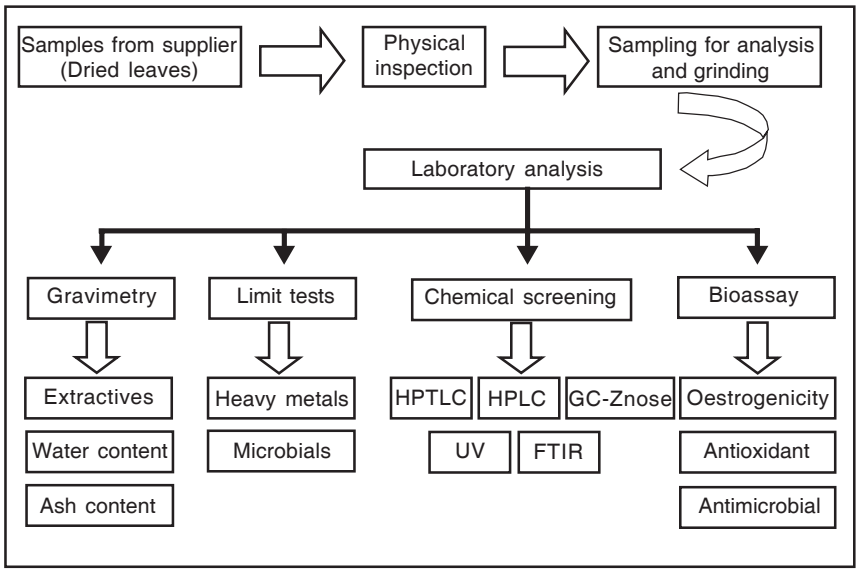



**Figure 4: Flow of quality control processes of raw materials of *Labisia pumila* var. *alata***




The leaves and roots of *L. pumila* var. *alata* were subjected to gravimetric analysis (Table 3); such as extractable matter, including cold water-soluble extractives using maceration and hot water-soluble extractives using reflux extraction; moisture content by the loss-on-drying method; and heavy metals (arsenic, lead, mercury and cadmium) using the atomic absorption spectroscopic method. In extractive analyses, it is revealed that substances are more easily extracted by soaking in hot water than through using the maceration technique, suggesting that heat encourages extraction of the water-soluble matter from *L. pumila* var. *alata*. This scientifically substantiates its traditional method of preparation by decoction. The plant was found to have a slightly high moisture content that could be associated with its natural growth habitat of shady and humid areas.

Thus, it is suggested that the raw plant materials should be thoroughly

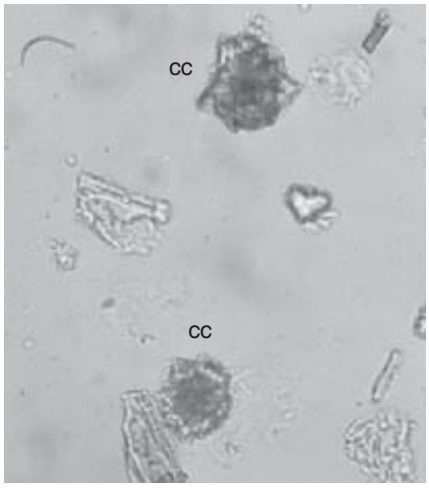
**Figure 5: (A) Voucher specimen of dried whole plant of *Labisia pumila* var. *alata*. The variety has broadly-winged leaf petiole. (B) Young plants of *Labisia pumila* var. *alata* cultivated away from its natural forest habitat. The plants usually take at least six months to mature.**

A

B

**Figure 6: Characteristic microscopical features of dried and powdered whole plant of *Labisia pumila* var. *alata*, observed under an optical microscope of x400 magnification factor, using liquid paraffin as a mounting agent. (A) Glandular multicellular peltate trichome. (B) Calcium oxalate cluster crystals (cc)**

A




B

dried prior to further processing, in order to protect it from deterioration by mould or bacterial growth, or by possible enzymatic or chemical hydrolysis of its active ingredients. The low level of heavy metals in *L. pumila* var. *alata* indicates that the plant may not be a potential metal accumulator, therefore, it may not potentially pose the risk of heavy metal toxicity in humans.

## Fingerprinting of raw materials

This study aims to establish qualitative chemical methods for the identification and authentication of its raw materials, so as to complement the pharmacognostical data, for the purpose of quality control. Chromatographic and spectroscopic analyses were performed on plant materials of *L. pumila* var. *alata* collected from ten different locations of West Malaysian forests. Thin layer chromatographic (TLC) profiles of the ethanolic (96 per cent) extracts were obtained using high-performance TLC (HPTLC) plates of silica gel F254 with $CHCl_3$-MeOH (10:1) as the mobile phase. Slightly different TLC band profiles were seen between the root and the leaf extracts (Figure 7).

Ultraviolet (UV) spectrophotometric spectra of the ethanolic (70 per cent) root and leaf extracts yielded absorption maxima of various intensities at maximum wavelength range of 278-280 nm and 280-282 nm, respectively (Figure 8). In addition, infrared (IR) spectrophotometric spectra of the raw powder of the roots and leaves (as potassium bromide discs) showed almost similar absorption band profiles; however, the leaf samples had distinct bands in the fingerprint region of 750-700 $cm^{1}$ (Figure 9).

TLC is most often used as a preliminary screening method to authenticate the identity of the plant materials based on their characteristic profiles ("fingerprints"). Other techniques such as high-performance liquid chromatography (HPLC), gas chromatography (GC), UV and IR have been used as tools to control the quality of herbal materials and products, owing to the fact that these techniques are accurate, sensitive and reproducible, as well as simple to operate and reasonably cheap. With recent advancements, more objective qualitative measurements can be made using chemometrical evaluation methods.[30, 31]

## Quantitative analysis

A preliminary phytochemical study successfully isolated a major component of benzoquinoid derivative which was chosen as a marker. The quantitative analysis was performed on the above samples, using HPTLC-densitometric analysis in $CHCl_3$-EtOAc (3:2). The data revealed that, in general, the root extracts (7.19-38.92 %w/w) had a higher content of marker component than the leaf extracts (0.00-10.93 %w/w).

The technique used in this study is applicable and reasonable for the quantification (assay) of marker compounds in *L. pumila* var. *alata*, especially when most of the other chemical components are unknown. However, other analytical techniques such as HPLC may be a more useful and reliable monographic method. Work is underway to establish the proper qualitative and quantitative evaluation using HPLC.

## Extraction methods for product development

The best method and parameters of extraction of the water extract of *L. pumila* var. *alata* was determined.[32] Laboratory-based methods of maceration, decoction, reflux and Soxhlet were used, whereas the parameters studied were temperature and duration of extraction. In general, the percentage of yield is higher for the root extract than the leaves; and that obtained from heating is higher than that obtained at room temperature. Based on the results, the ideal water extraction method and parameters (temperature and duration) for *L. pumila* var. *alata* are found to be the following: maceration (25°C, e" 6 h), decoction (60°C, d" 10 mins) and reflux (100°C, d" 4 h). Soxhlet was found to be the most ineffective method for laboratory extraction. Thus it can be suggested that large-scale extraction may be done under low temperatures at a reduced pressure, in order to obtain optimum yield - for example, using the supercritical fluid extraction (SFE) technique.

**Table 3: Limits of extractable matter (extractive), moisture content and ash, and content of heavy metals based on the data obtained from gravimetric analysis of the leaves and roots of *Labisia pumila* var. *alata***

| Gravimetric method | *Labisia pumila* var. *alata* % w/w | |
|---|---|---|
| | Leaves | Roots |
| Cold water-soluble extractive | e" 9% w/w | e" 12% w/w |
| Hot water-soluble extractive | e"13% w/w | e" 17% w/w |
| Moisture content (by loss on drying) | d" 11% w/w | d" 11% w/w |
| Total ash | d" 11% w/w | d" 11% w/w |
| Acid-insoluble ash | d" 1% w/w | d" 1% w/w |
| Water-soluble ash | d" 7% w/w | d" 3% w/w |
| Arsenic content | < 5 ppm | < 5 ppm |
| Lead content | < 10 ppm | < 10 ppm |
| Mercury content | < 0.5 ppm | < 0.5 ppm |
| Cadmium content | < 0.3 ppm | < 0.3 ppm |

**Table 4: Data of friability, disintegration time and dissolution rate of formulations containing water extract of *Labisia pumila* var. *alata***

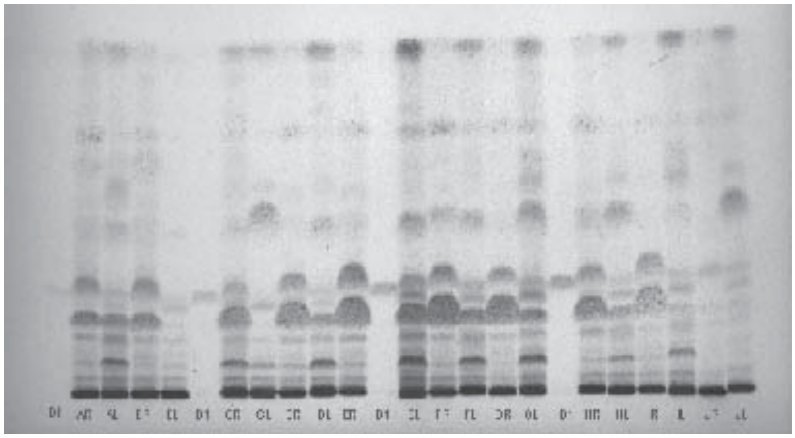
| Test methods | Formulations of *Labisia pumila* var. *alata* water extract | | |
|---|---|---|---|
| | Direct compression of freeze-dried extract | Direct compression spray-dried extract | Direct compression of freeze-dried extract |
| Friability (% w/w loss) | 0.92 | 0.75 | 0.67 |
| Disintegration time (mins) | 7.27 | 14.06 | 13.22 |
| Dissolution rate (mins for 70% release) | 5 | > 45 | 27 |

## Tablet formulation

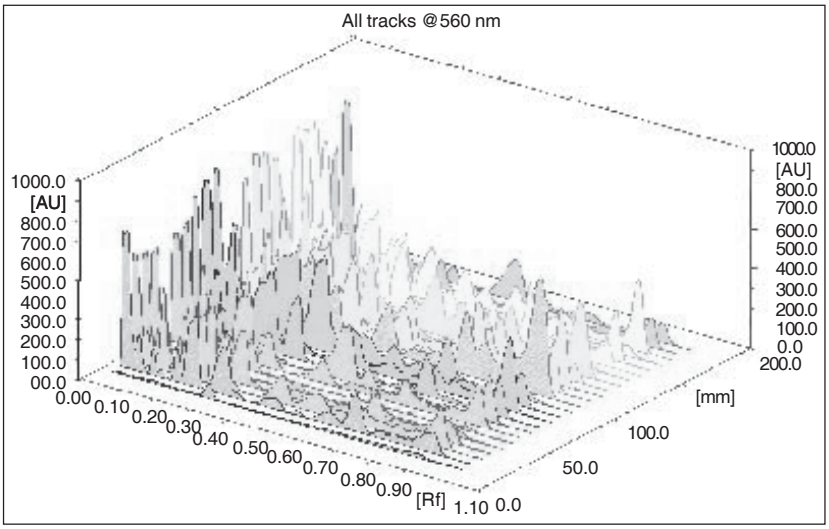
Several formulations containing the water-soluble freeze-dried or spray-dried extract of *L. pumila* var. *alata* and different excipients were prepared by either direct compression or wet granulation tabletting methods. According to the British Pharmacopoeial specifications, the tablet formulation is considered acceptable when it passes the performance tests of friability (maximum loss of 1 per cent), disintegration time (not less than 15 minutes) and dissolution rate (not less than 70 per cent in 45 minutes).

Using the direct compression method, a formulation containing the

**Figure 7: (A) Thin layer chromatographic (TLC) chromatogramme of the ethanolic (96%) extracts of *Labisia pumila* var. *alata* roots (R) and leaves (L) collected from various sites in Malaysian forests. The chromatogramme was obtained using high-performance TLC (HPTLC) plates of silica gel F254 with $CHCl_3$-MeOH (10:1) as the mobile phase. Observation was made under daylight after treatment with Anisaldehyde-sulphuric acid spray reagent. (B) Two-dimensional TLC chromatogramme of (A), showing the various types of chemicals and content as indicated by the peaks.**



**(A)**




**(B)**

freeze-dried water extract of *L. pumila* var. *alata*, microcrystalline cellulose, calcium lactate pentahydrous, Clearam CH20 (modified corn starch) and magnesium stearate were found to be acceptable (Table 4).[33] However, in this study, the utilization of corn starch, stearic acid and more than 25 per cent microcrystalline cellulose was found to decrease the dissolution rate of the extract. The spray-dried tablets prepared by the direct compression method failed the dissolution test, and the study suggested that the use of microcrystalline cellulose and Clearam CH20 were incompatible with the spray-dried extract.[34] In the wet granulation study, a formulation containing *L. pumila* var. *alata* freeze-dried water extract, polyvinylpyrrolidone, potato starch, magnesium stearate and lactose produced acceptable pharmaceutical performance.[35] However, the disintegration time and dissolution rate are greatly increased, as compared to the freeze-dried water extract tablets prepared using the direct compression technique.

From the study it can be concluded that the excipients used in the formulation and tabletting method can affect the performance of tablet preparation. At present, herbal medicinal products in tablet dosage forms, especially those containing freeze or spray dried extracts, are very limited in Malaysia. This could be due to the tedious R&D taken to acquire the optimum formulation. However, in the long run herbal tablet preparations are more cost effective than those prepared in hard gelatine capsules.

## Opportunities for business

The increasing demand for traditional medicinal products provides vast opportunities for SMEs. In Malaysia, an overwhelming awareness and interest by the general public have encouraged the herbal products industry. A further boost has come from governmental policies giving emphasis and priorities to sectors such as scientific R&D, agroindustry, manufacturing industry and trading activities. Many scientists from public and private universities and colleges, as well as research institutions, have great interest and are committed to natural or herbal products. However, not many of their research findings are being exploited. Here SMEs can tag along with particular groups of experts to commercialize their research concepts, as well as to rectify problems of producing "questionable" herbal products that lack scientific data and evidences.

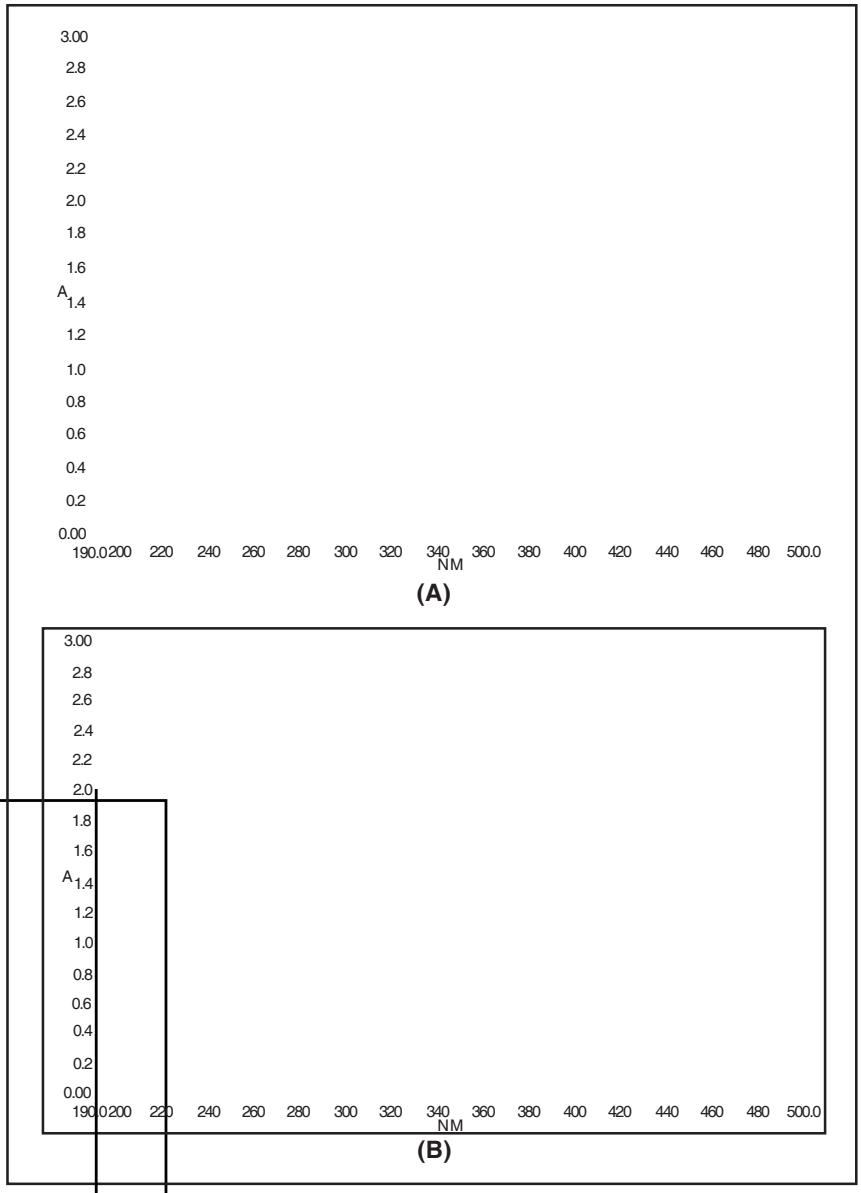
Other systematic approaches are suggested here:

- For a new herbal product, SMEs can first identify those types of herbals or species of medicinal plants with potential market value, based on either trend or popularity of use; or those that have been thoroughly-studied; or those with ethnobotanical uses (though this is currently not a popular basis).
- Retail or multi-level marketing businesses can be set up to provide means of selling TM, food and nutritional supplements directly to consumers. Properly registered and

permanent premise sites are encouraged so as to portray formalized business and prestige. In fact, most educated and professional consumers prefer to purchase products from such premises, because it would be easier for them to refer back in case of any problems. It is also highly recommended that only registered and non-expired traditional medicinal products are placed on the shelves, and that staff are properly trained and well-informed of the products, mainly for company reputation.

- Another most popular method of business is in trading activities (as importers, exporters or wholesalers). The companies either import or export and distribute raw materials to manufacturing industries, or repackage herbal ingredients into brand name products. It is highly recommended that these companies closely monitor the quality of the plant materials or ingredients, by either having their own quality control laboratories or sending to private laboratories for analysis, in order to reduce the risks of selling problematic products.
- SMEs can also manufacture their own herbal products. However, this would require extremely high capital for construction and maintenance of a GMP and Good Laboratory Practice (GLP) compliance premises and facilities, as well as proper human resources. Manufacturers must also consider long-term investments in scientific R&D to produce products of high quality, safe and efficacious, so that the output outweighs the expenses. SMEs in Malaysia can refer to organizations such as Malaysian Herbal Corporation (MHC) and Malaysian Organization of Pharmaceutical Industries (MOPI).
- On the other hand, SMEs can venture into cultivation and processing industries as suppliers of herbal raw materials. Particularly in Malaysia, this type of business is not well-developed yet, but SMEs should take up the opportunity, especially now that the government has put its focus on agroindustry. SMEs would require knowledge on Good Agricultural and Collection Practice (GACP) and Good Harvesting Practice (GHP) to ensure sustainable supplies of herbal materials of consistent quality. They can also seek help from specific research institutions. In Malaysia, these would be the Forest Research Institute of Malaysia (FRIM) and the Malaysian Agricultural Research and Development Institute (MARDI).

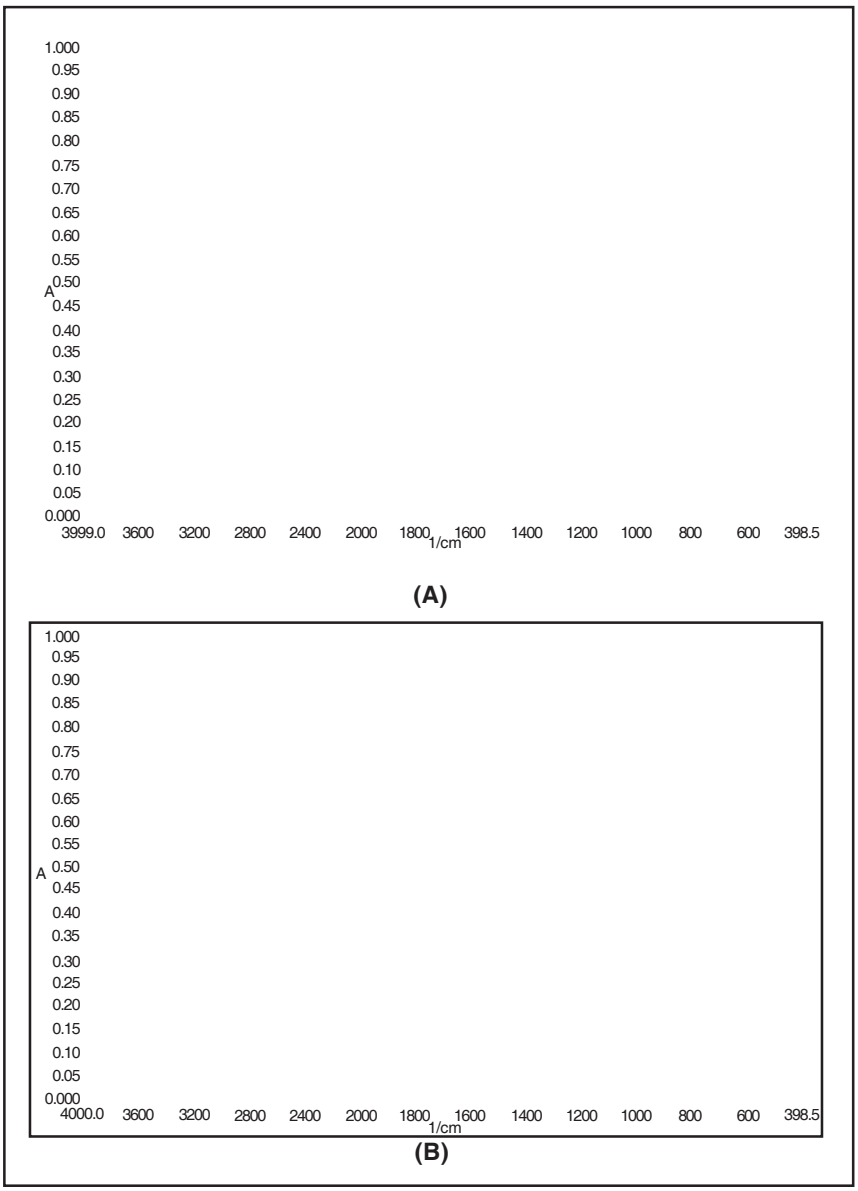
**Figure 8: Ultraviolet (UV) spectrophotometric spectra of the ethanolic (70%) extracts of *Labisia pumila* var. *alata* roots (A) and leaves (B) collected from various sites of the Malaysian forests.**




## Conclusion

In promoting the proper use of herbal medicinal products, a comprehensive programme of R&D, cultivation, production, trade and appropriate use in the community and healthcare sectors must be encouraged and supported. Thus a joint, coordinated and holistic effort among scientists, farmers, manufacturers, traders, health care professionals and regulatory authorities is required to drive the industry to comply with consumer expectations of quality, safety and efficacy in herbal products. Ethics should underlie personal and business interests, so as not to jeopardize the consumers' health.

**Figure 9: Fourier-transform infrared (FTIR) spectrophotometric spectra of the ethanolic (70%) extracts of *Labisia pumila* var. *alata* roots (A) and leaves (B) collected from various sites in Malaysian forests.**




## Acknowledgement

The author would like to express her sincere thanks and appreciation to Professor Dr. Zhari Ismail (School of Pharmaceutical Sciences, University of Science Malaysia), and Professor Dr. Ibrahim Jantan and Dr. Mohd. Cairul Iqbal Mohd. Amin (Department of Pharmacy, Faculty of Allied Health Sciences, National University of Malaysia) for their scientific contribution and support. The research on *Labisia pumila* var. *alata* was funded by the Malaysian Government through the IRPA programme (06-05-01-002 BTK/ER/013).

## References

1. Burkill, I. H. (1935). *Dictionary of the Economic Products of the Malay Peninsula*. Crown Agents, London.
2. Zakaria, M. & Mohd, M. A. (1994). *Traditional Malay Medicinal Plants*. Penerbit Fajar Bakti, Sdn. Bhd., Kuala Lumpur.
3. A. Samad, A. (2005). *Warisan Perubatan Melayu*. 2nd Edition. Dewan Bahasa & Pustaka, Kuala Lumpur.
4. Ridley, H. N. (1907). *Materials for a Flora of the Malayan Peninsula*. Methodist Publishing House, Singapore.
5. Gimlette, J. D. (1913). *Some Superstitious Beliefs Occurring in the Theory and Practice of Malay Medicine*. (Publisher unknown).
6. Gimlette, J. D. (1971). *Malay Poisons and Charm Cures*. Oxford University Press, New York
7. Gimlette, J. D. & Burkill, I. H. (1930). *The Medical Book of Malayan Medicine*. Botanic Gardens, Singapore..
8. Gimlette, J. D. & Thomson, H.W. (1939). *A Dictionary of Malay Medicine*. Oxford University Press, London.
9. Authur, H. R. (1954). A phytochemical survey of some plants of North Borneo. *Journal of Pharmacy and Pharmacology*, Vol. 6: pp 66-72.
10. Douglas, B. & Kiang, A. K. (1957). A Phytochemical Survey of the Flora of Malaya. I. Alkaloids. *Malayan Pharmaceutical Journal*, Vol. 6: pp 138-153.
11. Kiang, A. K., Douglas, B. & Morsingh, F. (1961). A Phytochemical Survey of Malaya. II. Alkaloids. *Journal of Pharmacy and Pharmacology*, Vol. 13: pp 98-104.
12. Amarasingham, D., Bisset, N. G., Millard, A. H. & Woods, M. D (1964). Phytochemical Survey of Malaya. III. Alkaloids and Saponins. *Economic Botany*, Vol. 18: pp 270-278.
13. Chan, K. C., Morsingh, F. & Yeoh, G.B. (1966). Alkaloids of *Uncaria pteropoda*. Isolation and Structures of Pteropodine and Isopteropodine. *Journal of Chemical Society (Perkin 1)*, Vol. 24: pp 2245-2249.
14. Ibrahim, J. (2004). Medicinal Plant Research in Malaysia: Scientific Interests and Advances. *Malaysian Journal of Health Sciences*, Vol. 2 (2): pp 27-46.
15. Mahmud, A. (1994). "Registration of Traditional Medicines in Malaysia" in Chan, et al. (eds.) *Trends in Traditional Medicine Research*. The School of Pharmaceutical Sciences, University of Science Malaysia, Penang, Malaysia. pp. 234-244.
16. Ibrahim, J. (2006). The Scientific Values of Malaysian Herbal Products. *Malaysian Journal of Health Sciences*, (*in press*).
17. Malaysian Herbal Monograph (1999). Vol. 1. Zhari, I., Norhayati, I.

& Jaafar, L. (contributors). Malaysian Herbal Monograph Committee, Kuala Lumpur.
18. Burkill, I. H. & Haniff, M. (1930). Malay Village Medicine. *Garden Bulletin of Straits Settlement*, Vol. 6: pp 165-317.
19. Abd.-Rahman, M. D. (1998). *Pengenalan dan Penggunaan Herba Ubatan*. Multi Triple Vision, Sdn. Bhd., Kuala Lumpur.
20. Stone, B. C. (1988). Notes on the Genus *Labisia* Lindl. (Myrsinaceae). *Malayan Nature Journal*. Vol. 42: pp 43-51.
21. Fasihuddin, A., Rahman, A. H., & Hasmah, R. (1995). "Medicinal Plants Used by Bajau Community in Sabah" in Chan et al. (eds.) *Trends in Traditional Medicine Research*. The School of Pharmaceutical Sciences, University of Science Malaysia, Penang. pp. 493-504.
22. Jamal, J. A., Houghton, P. J. & Milligan, S. R. (1998). Testing of *Labisia pumila* for Oestrogenic Activity Using a Recombinant Yeast Sceen. *Journal of Pharmacy and Pharmacology*, Vol. 50 (Supplement): pp 79.
23. Jamia, A. J., Houghton, P. J., Milligan, S. R. & Ibrahim, J. (2003). The Oestrogenic and Cytotoxic Effects of the Extracts of *Labisia pumila* var. *alata* and *Labisia pumila* var. *pumila* In Vitro, *Malaysian Journal of Health Sciences,* Vol. 1: pp 53-60.
24. Ibrahim, J., Young-Hwa, K., Dae-Yeon, S. & Byung, H. H. (1996). Inhibitory Effects of Malaysian Medicinal Plants on the Platlet-Activating Factor (PAF) Receptor Binding. *Natural Product Sciences*, Vol. 2 (2): pp 86-89.
25. Rasadah, M. A., Nik-Musa'adah, M., Aznie-Aida, A. & Mohd.-Rizal, A. K. (2001). "Inhibitory Activity of Some Selected Malaysian Medicinal Plants on TPA Induced Mouse Ear Oedema" in Ahmad Sazali et al. (eds.) *Fine Chemicals From Natural Resources*. University Publication Centre, University of Technology MARA, Shah Alam, Malaysia, pp. 371-376.
26. Houghton, P. J., Jamal, J. A. & Milligan, S.R. (1999). Studies on *Labisia pumila* herb and its commercial products. *Journal of Pharmacy and Pharmacology*, Vol. 51 (Supplmt): pp 236.
27. Jamia, A. J. & Houghton, P. J. (2000). "Alkenyl resorcinols from *Labisia pumila* var. *alata*" in *Natural Products Research in Malaysia 1999*. Pulau Pinang: Universiti Sains Malaysia, pp. 45-46.
28. Zainon, A. S., Musa'adah, M., Ismail, M. & Wan-Fadhilah, W. Z. A. (1999). "Ethnobotany of Medicinal Plants at Pos Lanai, Lipis, Pahang" in Mawardi et al. (eds.) *Interdisciplinary Approaches in Natural Products Research*. Department of Chemistry, Faculty Science and Environmental Studies, Universiti Putra Malaysia, Serdang, pp. 35-42.
29. Runi, S. P. (2001). "Studies on Medicinal Plant in Sarawak" in Chang et al. (eds.) *Towards Bridging Science and Herbal Industry*. Forest Research Institute of Malaysia (FRIM), Kuala Lumpur. pg. 112-119.
30. Dharmaraj, S., Suhaimi Jamaludin, A., Mohammad Razak, H., Valliappan, R., Nor Atinah, A., Harn, G. L. & Zhari, I. (2006). The Classification of *Phyllanthus niruri* Linn. According to Location by Infrared Spectroscopy. *Vibrational Spectroscopy*, Vol. 41: pp 68-72.
31. Razié, S., Onjia, A., Đogo, S., Slavković, L. & Popović, A. (2005). Determination of Metal Content in Some Herbal Drugs - Empirical and Chemometric Approach. *Talanta*, Vol. 67: pp 233-239.
32. Jamia, A. J., Azura, A. S., Khairana, H., Ibrahim, J. & Mohd. Shahidan, M.A. (2006). Pelbagai Kaedah Pengekstrakan Air *Labisia pumila* var. *alata*. *Malaysian Journal of Health Sciences,* (*in press*).
33. Ching, M. W. (2005). Pembangunan Satu Formulasi Tablet yang Mengandungi Ekstrak Larut Air Pengeringan Sejuk-Beku *Labisia pumila* var. *alata* Secara Pemampatan Terus. B. Pharm. (Hons) Thesis. National University of Malaysia, Kuala Lumpur.
34. Lim, S. P. (2004). Pembangunan Satu Formulasi Tablet yang Mengandungi Semburan Kering Ekstrak Larut Air *Labisia pumila* var. *alata* Secara Pemampatan Terus. B. Pharm. (Hons) Thesis. National University of Malaysia, Kuala Lumpur.
35. Sumaiyyah, S. (2006). Pembangunan Satu Formulasi Tablet yang Mengandungi Ekstrak Larut Air Pengeringan Sejuk-Beku *Labisia pumila* var. *alata* Secara Penggranulan Basah. B.Pharm. (Hons) Thesis. National University of Malaysia, Kuala Lumpur.
36. Farnsworth, N. R. & Soejarto, D. D. (1992). "Global importance of medicinal plants" in Akarele et al. (eds) *Conservation of medicinal plants*. Cambridge University Press. pp. 25-51.

## WHO References

- WHO (1993). Guidelines on the Conservation of Medicinal Plants. WHO, Geneva.
- WHO (1996a). Annex 11. Guidelines for the Assessment of Herbal Medicines. WHO, Geneva.
- WHO (1996b). Annex 08 - Good Manufacturing Practices : Supplementary Guidelines for the Manufacture of Herbal Medicinal Products. WHO, Geneva.
- WHO (1998a). Quality Control Methods for Medicinal Plant Materials. WHO, Geneva.
- WHO (1998b). Basic Tests for Drugs - Pharmaceutical Substances, Medicinal Plant Materials and Dosage Forms. WHO, Geneva.
- WHO (2003a). Traditional Medicine. WHO, Geneva.
- WHO (2003b). WHO Guidelines on Good Agricultural and Collection Practices (GACP) for Medicinal Plants. WHO, Geneva.
- WHO (2004). WHO Guidelines on Safety Monitoring of Herbal Medicines in Pharmacovigilance Systems. WHO, Geneva.
- WHO MD (2000). General Guidelines for Methodologies on Research and Evaluation of Traditional Medicine. WHO, Geneva.
- WHO/TRM (1998). Regulatory Situation of Herbal Medicines - A Worldwide Review. WHO, Geneva.
- WHO/WPRO (1993). Research Guidelines for Evaluating the Safety and Efficacy of Herbal Medicines. WHO Regional Office for the Western Pacific, The Philippines.
- WHO/WPRO (1998). Guidelines for the Appropriate Use of Herbal Medicines. WHO Regional Office for the Western Pacific, The Philippines. ❐