PHYTOCHEMICAL PROCESSING: THE NEXT EMERGING FIELD IN CHEMICAL ENGINEERING - ASPECTS AND OPPORTUNITIES

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ABSTRACT

Phytochemical processing is an area of engineering that is critical to the growing multi million dollar global business of healthcare in pharmaceutical, nutraceutical, and herbal based industries. This article covers the global and national business outlook of this budding industry, the potential crops to be commercialised in Malaysia, critical areas for chemical engineers to be involved in, and overviews on some work done at the Chemical Engineering Pilot Plant in Universiti Teknologi Malaysia.

INTRODUCTION

The herbal related market includes herbs used as food or food additives, cosmetic ingredients, and herbal medicines. The current estimates for this market ranges between USD 40-100 billion with an average annual growth rate of 15 to 20% (Merican 2003 and Exim Bank 2003). Malaysians have consumed RM 2 billion worth of herbal products in 1997, which was double the amount spent per person as compared to consumers in the US (Merican 2003) These statistics show the significance of this industry.

Dr. Paul Zane Pilzer (2001), in his book entitled 'The Next Trillion' values the US healthcare industry to be above 1 trillion dollars for both pharmaceutical and food based products each. He predicts that the spending will shift from illness oriented products, such as pharmaceuticals, to wellness promoting products, such as herbs and nutraceuticals. Table 1 lists out several common forms of herbal related products and their commonly accepted definitions.

A significant portion of this market are medicinal products from plant sources. Many allopathic medicines, which are produced synthetically, are also derived from plants such as quinine for malaria and quinidine for hearth arrhythmia from *Cinchona* spp, and digoxin for heart failure from *Digitalis* spp. About 25% of drugs prescribed worldwide come from plants, 121 such active compounds being in current use (Rates 2001).

Table 1: Common Herbal Products

PHYTOCHEMICAL – comes from the Greek word "Phyto" for plant. It refers to every naturally occurring chemical presents in plants. Plant are also the source many modern pharmaceutical (drugs). It is estimated that approximately one quarter drugs contain plant extract or active ingredients obtained from plant substances.
COSMECEUTICAL – is the term used to describe cosmetic containing ingredients that are bioactive, exerting effects on people. It is a blend of cosmetic and pharmaceutical which has appeared only in the nineties. Examples are anti-wrinkles creams, baldness treatments, moisturizers and sunscreens.
NUTRACEUTICAL – can be any substance that may be considered a food or part of a food that provide medical and health benefits, including the prevention and treatment of disease. Under this broad definition, nutraceutical might be isolated nutrients, dietary supplements or diets, processed foods, herbal products or genetically engineered "designer foods".

OLEORESIN – are pure extractives of a spice or herb which contain concentrated natural liquid flavourings that contain both volatile and non-volatile flavour components.

ESSENTIAL OILS – volatile part of the plant that are largely responsible for its characteristic aroma. It can be applied to enhance health through its holistic effects on the body.

There is a growing trend of people moving from synthetic allopathic drugs to herbal cures. Among reasons for this shift include a preference for a wellness oriented self administered healthcare, the prevalence of chronic illnesses that cannot be cured by conventional drugs, and the fast pace of life which induces higher stress and reduced free time.

In view of the potential size of the herbal based market, and herbal medicines in particular, it is important that Malaysia builds an industry based on its natural herbal heritage. Process technology therefore needs to be developed for the phytochemical industry.

Global Trends in Herbal and Nutraceutical Products

The global herbal market is valued at USD 70 billion for nutraceuticals and USD 20 billion for phytomedicines with an average annual growth rate between 15 to 20% (Exim Bank 2003, Gruenwald and Hezberg 2002, and Sloan 2002). Among driving forces for the growth of the global herbal industry include:

- Population demographics – a large portion of the developed nations are older, thus higher demand for anti aging and chronic disease cures
- Increasing focus on health versus disease
- Drive towards self care and self diagnosis

A key driving force is the growing knowledge of consumers about traditional medicines. Many consumers have come to realise that effective herbal cures are the results of thousands of years of herbal healing framework developed through trial and error, observation, and study. Also, there have been some high profile natural based cures such as *Taxol* for breast cancer and the *Bintangor* plant for AIDS.

In several countries, traditional healing methods have been incorporated into the modern health system. In Germany, herbs which are proven to be safe and effective are readily incorporated into the medical system (Murray 1999). In Japan, doctor prescribed phytomedicines can be claimed under national health insurance (Kenner 2001).

A key sub area of the herbal industry that is growing rapidly is the nutraceutical area (Sloan, 2002 and Gruenwald and Hezberg, 2002). Consumers are showing a growing preference to consume their nutritional needs through their food rather than in a medicinal form such as capsules or tables. Among key items are fortified foods such as grains fortified with calcium or vegetables fortified with herbal extracts such as *Gingko Biloba.* In France and Germany, *Gingko Biloba* has total sales of USD500 million dollars as a treatment for cerebral and peripheral vascular insufficiency (Murray 1999).

The Malaysian Herbal Industry Scenario

Malaysia is well positioned to be a key global player in the herbal medicine industry with its rich biological heritage, cultural background and trade links (Arif 2002). Malaysia is listed as the 12th most bio-diverse nation in the world and 4th in Asia with over 15,000 flowering plants and over 3000 species of medicinal plants (Adenan 2003). Of the 3000 listed medicinal plants, only about 50 are used and even less are being researched scientifically for their medicinal properties, and many more have yet to be catalogued extensively through ethno botanical research.

Malaysia is also home to 3 major races, Malays, Chinese and Indians, as well as a host of diverse indigenous groups, who all have a rich tradition and knowledge of herbal use for health and healing. At present, the Malaysian market for herbal products has been estimated to be worth RM4.55 billion with a growth rate of 15 to 20% of which 90% of the raw material used was imported (Puteh 1999). The key driving forces in the Malaysian domestic market are the changes in lifestyle, the growing emphasis on health, and the growing cost of synthetic medicines.

The Malaysian government has been strongly supportive of the development of a Malaysian herbal industry. The National Agricultural Policy (1998-2010) identifies a product and export oriented policy as a thrust area. Herbal cultivation easily falls under this category. In addition, the Ministry of Health in 1999 has released a Traditional/Complimentary Medicine (TCM) Policy with the emphasis of 'rational use', the philosophy that traditional as well as modern medicines can be used concurrently.

On the industrial front, the Malaysian Herbal Corporation (MHC) was formed under the auspices of the Malaysian Industry – Government Group for High Technology (MiGHT) in 1998 to coordinate the efforts to build up the local herbal industry between the private and public sector. It is specifically aimed to address critical issues along the herbal value chain as shown in Figure 1 to allow the industry to become globally competitive.

The Malaysian government has also given financial support to research work related to herbs in term of Intensified Research in Priority Areas (IRPA) grants, the focus areas by the National Biotechnology Directorate, as well as other grant schemes. Areas of focus include ethnobotany, phytochemicals, processing, cultivation studies, biochemistry, pharmacology, and clinical trials.

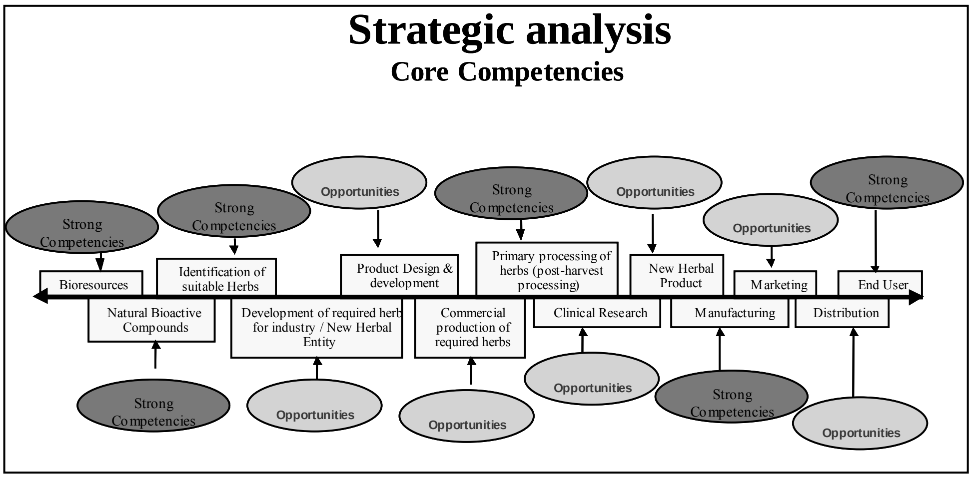

FIGURE 1 MiGHT Analysis of Herbal Industry in Malaysia (Wazir 2003)

Another issue that the Malaysian Government will need to address is the issue of Intellectual Property Rights with regards to herbal value in terms of indigenous species and traditional usage. The recent cases involving tumeric and neem where India successfully challenged the patents filed by the US highlights the danger in not taking active steps to protect local knowledge and plants (Shiva 2000).

A CROSS SECTION OF COMMERCIALLY VIABLE MALAYSIAN HERBS

Tongkat Ali, *Eurycoma longifolia* (Figure 2a), is a traditional Malay and *Orang Asli* herb used as an aphrodisiac, general tonic, anti-Malarial, and anti-pyretic. Scientifically it has also been found to have anti-tumour and anti oxidant properties. The decoction of the roots is taken orally. It has been biochemically shown to increase testosterone production as well as to overcome impotence

Kacip Fatimah, *Labisia pumila* (Figure 2b), is a herb used in the treatment of post partum mothers, gonorrhoea, rheumatism, pile, and bone diseases. It is currently being researched for its estrogenic and androgenic properties. If found to be viable, it will represent a good herbal medicine for hormone replacement therapy or estrogen related therapy. The Chemical Engineering Pilot Plant (CEPP) together with Universiti Malaysia Sabah is involved in preparing water extracts for clinical studies for a national top down research project.

Hempedu Bumi, *Andrographis paniculata* (Figure 2c), is used for anti-pyretic, anti-fertility, treatment of appetite loss, anti-diabetes, anti-hypertensive, and skin condition – eruption and scabies. In traditional use its leaves are boiled and taken as an oral decoction. It has a very bitter property and is a strong liver tonic. Universiti Sains Malaysia (USM) researchers have studied its anti diabetic and anti hypertensive properties in order to produce herbal medicines.

FIGURE 2 (a) Tongkat Ali ; (b) Kacip Fatimah ; (c) Hempedu Bumi

Misai Kucing, *Orthosiphon stamineus* (Figure 3a), can be used for kidney related and joint ailments such as gall stones, diabetes, arthritis, rheumatism, and gout. It has been proven to remove uric acid through its diuretic activity which is the main path for its therapeutic activity. CEPP also works with USM in producing the herbal extracts for pharmaceutical studies of Misai Kucing.

Pegaga, *Centella asiatica* (Figure 3b), is a long used Asian herb mentioned in both the Chinese Materia Medica and Ayurvedic texts for its anti aging and overall beauty enhancement properties. It works by enhancing the connective tissue activity in the skin. It is cultivated on a large scale by French Cosmetic companies as an ingredient in cosmetic products. Pegaga is also one of the plants studied under the Malaysia-MIT Biotechnology Partnership Programme apart from Tongkat Ali.

FIGURE 3 (a) Misai Kucing ; (b) Pegaga

FROM PLANTING TO PRODUCT: THE HERBAL VALUE CHAIN

There are several major steps in herbal product manufacturing starting from herbal crop planting to herbal product manufacturing and marketing. Chemical engineers are involved once the herb is harvested where quick preprocessing and correct storage is required. Preprocessing involves reducing the size of the herb through chopping and grinding to prepare for processing while good storage method ensures that the active phytochemicals are maintained before processing.

Processing is a critical aspect of herbal production, especially due to the low yield of extracts. Processing methods are usually based on traditional methods such as high pressure water extraction for herbs which are traditionally boiled as decoctions. New innovative methods such as Supercritical Fluid Extraction (SFE) where supercritical fluids such as carbon dioxide under high pressure are utilised to produce herbal extracts need to be developed to produce herbal products of higher yield, lower operating costs, and faster production times. Packaging and sale follow processing. Herbal products can be sold in a variety of forms such as capsules, tablets, tea bags, extracts and essential oils.

Good Manufacturing Practice (GMP) is a code of practice used by the medical and health related industries including the pharmaceutical industry in an effort to maintain the highest standards of quality in the development, manufacture and control of medicinal products. In Malaysia, the GMP certification is issued by National Pharmaceutical Control Bureau (NPCB), which is issued as an annual Manufacturing License to which it can be revoked at any time if the facilities are found not to meet the standards of GMP. Herbal medicine products can only be sold by manufacturers who utilize GMP as it ensures that the herbal product safety and purity. In addition, manufacturers intending to export their products must ensure that their target markets accept their GMP practices.

A key issue in manufacturing herbal products and medicines is standardisation. Standardisation is the process of producing herbal extracts or phytochemicals in which product potency is guaranteed through consistency in active compound content level. This process requires high knowledge in phytochemical analysis and process technology to ensure the quality assurance required. Figure 4 shows the increase of value in herbal products as increased processing and standardisation is carried out.

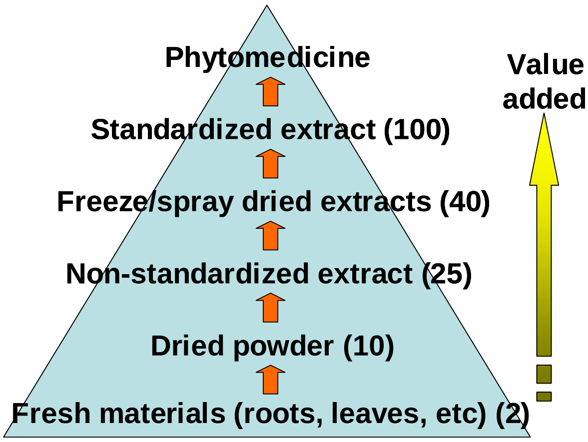

FIGURE 4: Increasing value of herbal products with processing and standardisation (Ismail 2003)

Herbal products can be sold in either whole herbal extracts or pure phytochemicals as shown in Figure 5. Engineers are involved in either whole herbal extracts or in mass transfer separation and purification steps to produce pure phytochemicals. In general it has been found that whole herbal extracts are more effective that isolated phytochemicals due to a synergistic effect between the phytochemical components. Therefore in standardisation, it is important to assure that the herbal phytochemical profile is maintained.

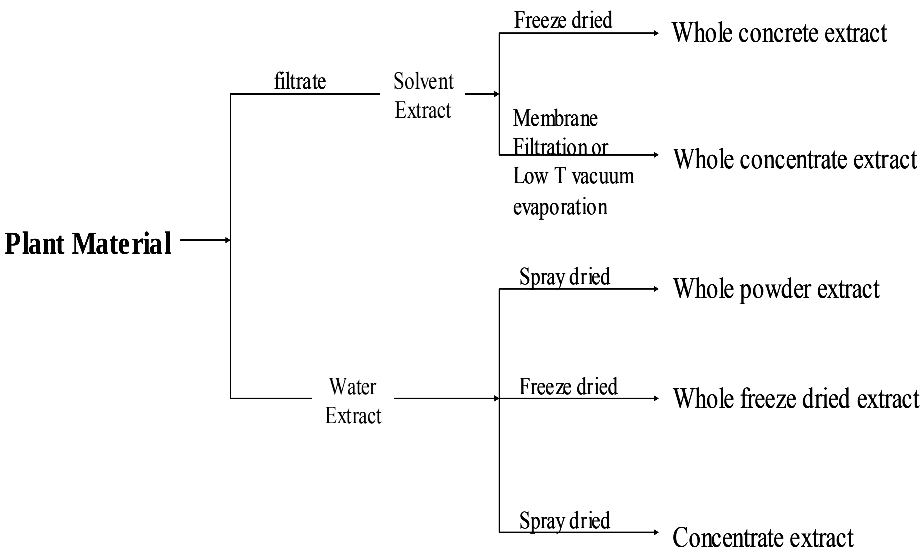

Figure 5 (a) Herbal Approach in Processing Herbal Products

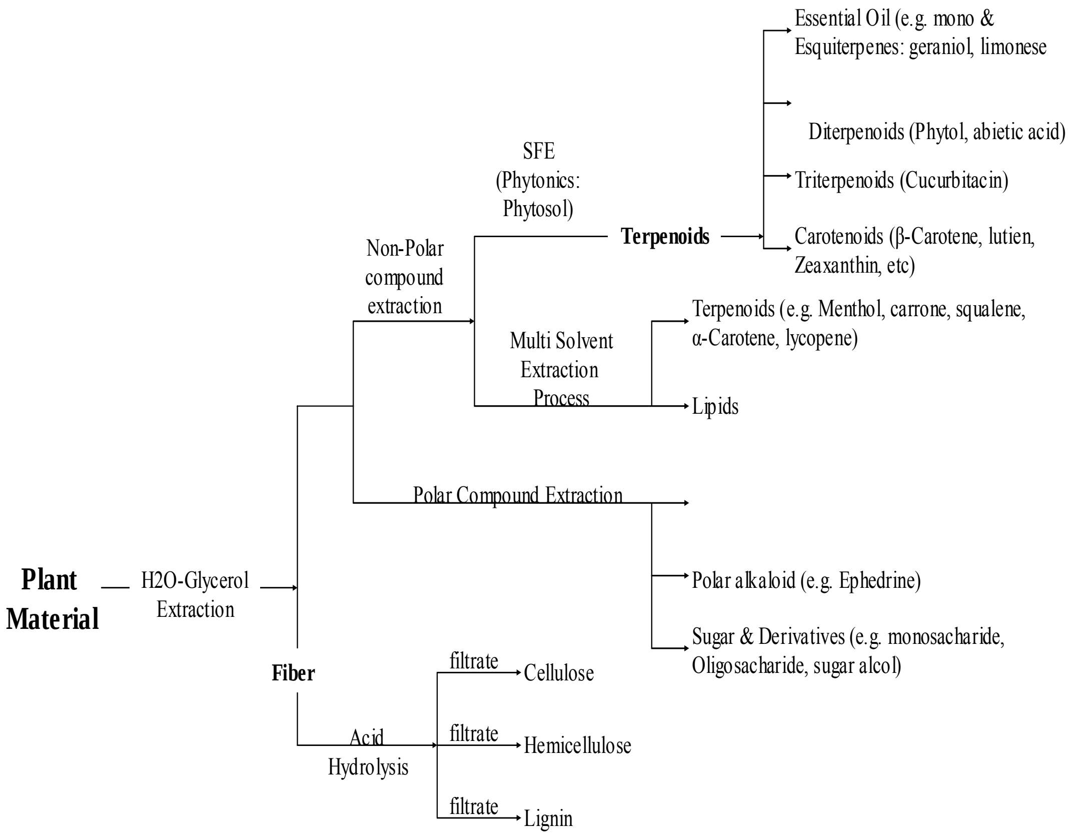

FIGURE 5 (b) Phytochemical Approach in Processing Herbal Products

THE ROLE OF CHEMICAL ENGINEERS IN THE PHYTOCHEMICAL INDUSTRY

Knowledge is the key catalyst in enabling Malaysia to become a global herbal producer. Process knowledge is a key area in chemical engineering that needs to be addressed. Phytochemical processing is a relatively new field of which chemical engineers and food technologists have been involved with only recently. As standardization is an important aspect of increasing value of phytomedicines, processing technology innovation as well as process operating information is required for local herbs. Important areas needed in research include the development of environmentally friendly processes, the application of new and novel processing methods to local herbs, and the enhancement of existing process technology.

In addition, as the overall phytochemical yield of herbal extracts are between 2-5 %, it is important to develop expertise in optimising the process as process profitability can be increased through:

- Reduction of utilities usage
- Increase in phytochemical yield
- Reduction of extraction solvents
- Reduction of processing time

Many processes within the phytochemical industry are similar or identical to unit operations within chemical engineering. Table 2 shows the similarities in terms on unit operations and phytochemical processing methods between traditional chemical engineering and phytochemical processing.

From Table 2, it can be seen that many areas of chemical engineering would be applicable to the phytochemical industry. In terms of basic knowledge Chemical engineers will need to focus on acquiring more knowledge on:-

- Organic Chemistry – Natural products chemistry in particular
- Analytical Methods – such as HPLC, LC-MS, NMR
- Separation Technology – such as SFE, natural product isolation and purification

As much research in phytochemical processing has been done by chemists in terms of chemical isolation and pharmacists in terms of bioactivity, there is a need for basic chemical engineering oriented research to be done. There are almost no data available on the physical and chemical properties of the phytochemicals or herbal medium to be processed, hence, process design and optimisation is currently a trial and error procedure. There is also a strong need to build up scale up knowledge, either through a theoretical basis or pilot plant experiments, as frequently only laboratory data is available.

Among key problems that must be addressed include developing process design knowledge for herbal extraction. Currently, much herbal extraction design is done based on knowledge from food technologists. Often these design methods do not take into account chemical thermodynamic data or design methods. Process models are built are not easily replicated or utilised as many are based on surface response methodologies which are only applicable to the equipment investigated. More first principle modelling methods need to be developed to model, optimise, and scale up herbal extraction processes.

Chemical Engineers will also need to work closely with other professionals in this new field with a new jargon and orientation. It is a cross disciplinary field that will involve phytochemists, food technologists, and pharmacists.

TABLE 2 Phytochemical Processing and Chemical Engineering Similarities

Unit Operation	**Chemical Engineering**	**Phytochemical Processing**
Mass Transfer	• Distillation • Solid Liquid Extraction • Supercritical Fluid Extraction	• Essential Oil extraction • Herbal leaching • Supercritical Fluid Extraction
Process Design	• Model based design • Process synthesis and design • Optimisation	• Model based design • Process synthesis and design • Optimisation
Bioprocess Engineering	• Downstream processing • Scale up	• Phytochemical approach • Scale up
Powder Technology	• Mixing	• Capsule preparation
Instrumentation and Measurement	• On line analysis • Process Control	• Phytochemical analysis • Process Control
Environmental Engineering	• Pollution prevention through substitution • Biomass conversion • Waste reduction	• Solvent design and substitution • Biomass conversion • Waste reduction

CEPP FOCUS ON PHYTOCHEMICAL PROCESSING

The Chemical Engineering Pilot Plant (CEPP) at Universiti Teknologi Malaysia (UTM) was set up in 1998 for the following objectives:

- To bridge the funding gap between research findings and commercialised products
- To assist Malaysia in building indigenous products and processes
- To assist Malaysia in building up indigenous expertise

Phytochemical processing was chosen as a focus area in the Fine Chemical section at the Pilot Plant. The primary emphasis in this area is on improving processing techniques for local herbal products as well as developing products for market testing as well as small scale production.

Several major equipment used for phytochemical processing include:

- 300 litre Extraction vessel for producing extracts
- Low Pressure Super Critical Extractor, a novel supercritical extraction process that uses Tetrafloroethane as a supercritical fluid which requires a lower pressure than carbon dioxide
- Hydro distillation unit for essential oil production
- Spray Dryer for herbal extract production
- Freeze Dryer for herbal extract production
- Centrifuge for concentrating and separating extracts
- Homogenizer for mixing extracts
- Turbo Extractor Distiller, an extractor that combines a grinder, extractor and distiller which can be used in producing essential oils more efficiently

As the analysis of the raw material, herbal extract, pure phytochemical and final products are critical to quality assurance and process development, several analytical equipment are available at CEPP which comprise of:

- High Performance Liquid Chromatograph (HPLC)
- Liquid Chromatography – Mass Spectrometer
- Spectrophotometer

Significant CEPP Research Projects and Industrial Collaborations

In the short time since it's formation in 1998, CEPP has been involved in several projects which include:

1. MHCP production from Cinnamon
2. Phytochemical production from *Zingiber Zerumbet* and *Curcuma Xanthorhizza*
3. Production of oleoresins and essential oils from *Zingiber officinale*
4. Tongkat Ali production process development
5. Aromatherapy product development
6. Vitamin E product formulation

A key concept in many of CEPP's projects is the biorefinery concept where raw plant material is totally fractionated and converted into a spectrum of valuable products. Cinnamon (kayu manis), a common spice used in Asian cooking, is one such plant where this concept can be applied. Among products from Cinnamon include essential oils, oleoresins, extracts, and purified phytochemicals. One high value product from Cinnamon is Methyl Hydroxy Chalcone Polymer (MHCP), a phytochemical with scientifically proven anti diabetic properties. MHCP has been found to increase cellular glucose oxidation by a factor of up to 20 fold, improve the function of insulin receptors in cells, and has a strong anti-oxidant effect (Anderson and Schmidt 2002).

An IRPA funded project entitled 'Production of Speciality Phytochemicals from *Cinnamomum Zeylanicum'* CEPP together with the UTM Science faculty as well as industry collaborators started in 2002. Its primary aim was to develop an environmentally safe and economically viable process to produce standardised Cinnamon extracts and purified MHCP. These extracts would be then used as functional food additives or phytomedicines.

Apart from Cinnamon, CEPP has also been involved in the production of phytochemicals from members of the *zingiberase* (ginger) family, *Zingiber Zerumbet* (lempoyang) and *Curcuma Xanthorrhiza* (temu lawak). Another IRPA funded project together with the Science faculty and industry collaborators was started in 2001 to develop process design to extract these two species. The active ingredients in Lempoyang and Temu Lawak are zerumbone, which has anti viral and potentially anti HIV properties, and xanthorrizol, which has anti bacterial properties. The process design project involves process detailed design, scale up studies, total plant utilisation through biorefinery approach, and phytochemical purification. An example of the Turbo Extraction Distillation device and its applications is shown in Figure 6.

Another product from the ginger family developed at CEPP are the essential oils and oleoresins from the household ginger, *zingiber officinale*. Ginger is freely available in Malaysia at a low price, therefore value added products can increase the value of this crop. In addition, many traditional cures in Malay, Indian, Chinese, and Indigenous groups are based on ginger (Ahmed and Sharma 1997). In collaboration with Universiti Malaysia Sabah, CEPP focused on the process design, process optimisation, and product commercialisation of essential oil and oleo resin production from ginger.

Besides IRPA funded projects, CEPP also focuses strongly on industry based development projects. A key and visible success process development at CEPP is the development of the Tongkat Ali water extract production process, which is currently utilised by Phytes Biotek Sdn Bhd and the Forest Research Institute of Malaysia (FRIM). Phytes Biotek, the country's first Malaysian Venture Capital (MAVCAP) investment, is currently the largest commercial producer of Tongkat Ali extracts

FIGURE 6 The Turbo Extractor Distiller and Its Specialty Chemical Products

Tongkat Ali extraction by Phytes Biotek previously had an extraction time of over 4 hours and low yield. After process development at CEPP, it was found that high pressure and temperature extraction increased the yield and reduced the extraction time to 2 hours. The process developed is shown in Figure 7 and Figure 8.

Apart from herbal extracts such as Tongkat Ali, CEPP has also developed aromatherapy products, as shown in Figure 9. CEPP has helped created several formulations in different forms such as lotions, sprays, and candles. A successful set of formulations are currently being marketed by Fyto-Elegance, another MAVCAP funded company.

CEPP has also done product formulations for spray dried Vitamin E from Palm Oil sources. The product formulation proved to be of high demand in countries such as Japan where in powder form it proved to be easily formulated and standardised.

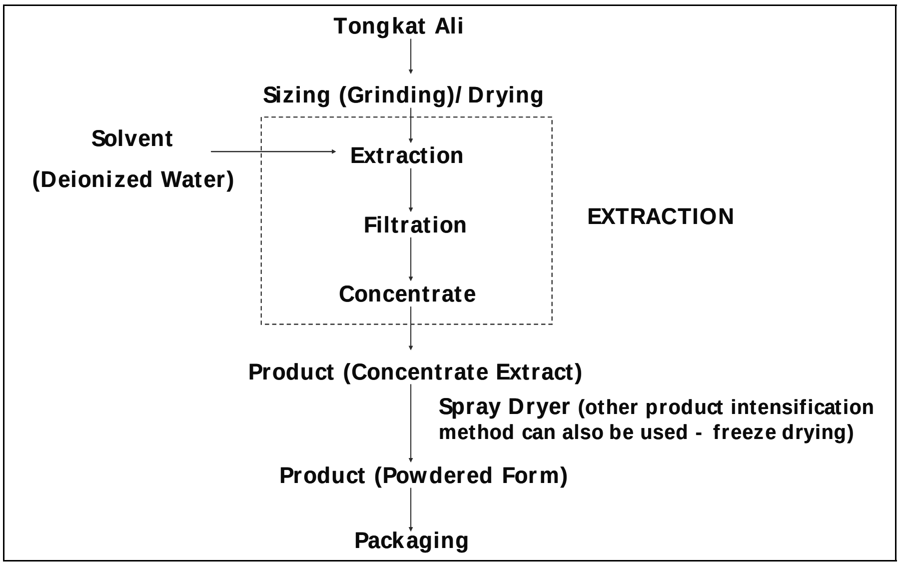

FIGURE 7 Tongkat Ali Process Flow Chart

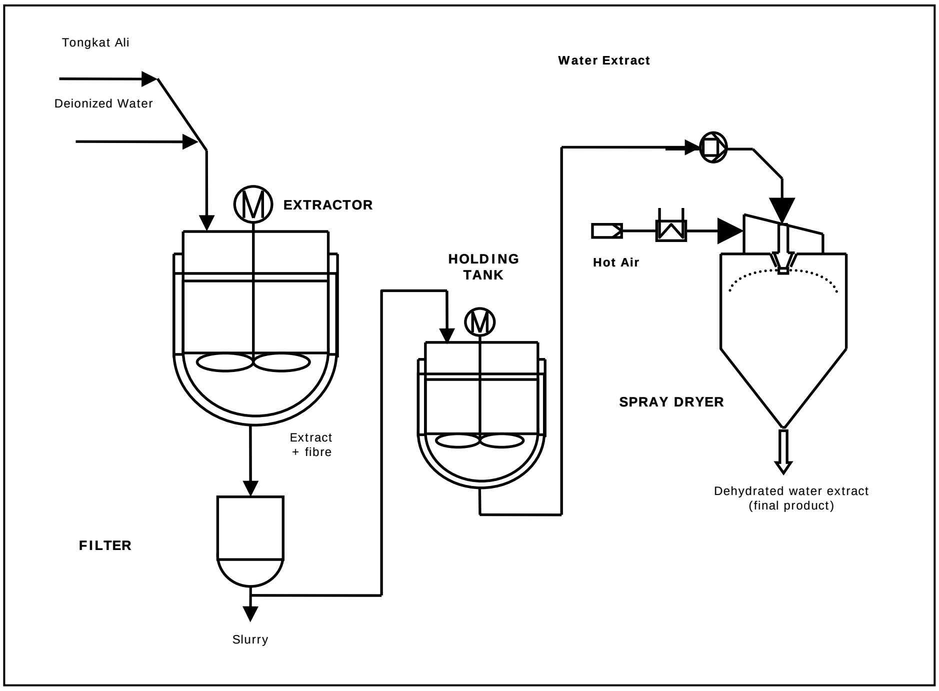

FIGURE 8 Tongkat Ali Water Extract Process Design

FIGURE 9 Aromatheraphy products developed at CEPP

Future Work at CEPP

In essence, CEPP intends to continue to pursue work focused on product and process development based on national natural resources through sustainable process technology.

A key area of focus will remain the Biorefinery approach where whole plant material is utilised to produce high value chemicals. In addition, as the health based industry is expected to continue growing at a high rate, more healthcare product and process development work will be pursued such as functional food additives. Lastly, as the knowledge base of the nation's human resources will be the driving force to the nations economic growth, CEPP will continue to develop more courses and trainings to serve the nations needs.

CONCLUSION

Phytochemical processing promises to be a lucrative industry for the future with a growth rate of 15 to 20 % of this almost USD100 billion business. Chemical Engineers are ideally suited to contributing to this industries growth with their process knowledge which can contribute to both process and product development based on the rich biological heritage of Malaysia.

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