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BIOLOGICALLY ACTIVE SECONDARY METABOLITES FROM MEDICINAL PLANTS

(Metabolit Sekunder Aktif Biologi Tumbuhan Ubatan)

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ABSTRACT

Plants have sustained the life of man since the beginning of the time. Their functionalities go beyond being wood for fire, instead, they are able to protect, provide and nourish. The many purposes of plants have been described by many. In this article, we will describe functional plants through the chemical perspective particularly the biologically active secondary metabolites. The initiatives in natural products studies can be traced to the early years of man when plants were used for health and treatment management as documented in traditional *materia medica*. In modern days, numerous phytochemicals have become the main ingredients in drugs, foods, cosmetics and many more after detailed and rigorous research programs which determine their safety and efficacy. In Malaysia, and Sabah in particular, efforts are planned and carried out to identify potential traditional plants that will be beneficial in their truest forms.

Keywords: traditional plants; natural products chemistry; functional foods; drug discovery

1. Phytochemistry in Functional Plants

A long time ago, the order of the day was for survival. During those days, man would do anything in order to survive. Through sheer bravery, brilliant ingenuity and sometimes ridiculous stupidity but very often miraculous serendipity, Man coped with daily obstacles such as cold and hot climate, hunger, predators, illnesses, and many more. They learned to build shelters to protect themselves from the sun or snow, to search for food by hunting animals and gathering plants, protecting themselves with clothes and armour and so forth. Fortunately, early humans were resourceful, since they have learnt to use what surrounded them. The main source was probably plants. Plants have helped to sustain man's life since the beginning, from covering up themselves with leaves, to building shelters with woody branch and broad leaves, to traveling in wooden canoes from one place to another. They provide us with the oxygen that we breathe in, the grain that we eat for energy and fruits and vegetables for our daily nutritional requirement as well as for healing and treating aids in addition to maintaining health. Thus, plants have played a big role in determining the success of man's

adventure since the beginning of time and will continue to be useful in the future. They have been domesticated in many forms, either on a small or industrial scale.

Phytochemistry is the study of chemical compounds form by biosynthesis in plants from secondary metabolism for functional purposes such as reproduction, defence etc. Those who are in the field carry out investigations of isolation, structural elucidation, determination of biological activities and synthesis of secondary metabolites. They may be experts from botany when they are interested in the chemotaxonomy of families for plants or, organic chemistry, for those who dwell in medicinal chemistry. However, most interesting would be drug discovery from medicinal plants as historical aspects provide vital information. These fascinating organic compounds are compelling in all regards; structurally, properties and application. In general, there are four main classifications of secondary metabolites; alkaloids, glycosides, polyphenols and terpenes (Saxena, Saxena, Nema, Singh, & Gupta, 2013).

2. Biologically Active Traditional Medicinal Plant Chemistry

In an annual conservation report in 2016, there are approximately 374,000, species of plants on earth, which are either flowering or non-flowering (Christenhusz & Byng, 2016). Numerous non-scientific and scientific reports have provided information regarding therapeutic properties of plants. A lot of these plants are yet to be explored, where only a small fraction had been studied for their chemical and biological activities, to determine their functionalities, safety and efficacies. This information will benefit the local communities who are practising traditional knowledge in their health management in term of ensuring proper diet with adequate and sustainable supply (Ripen & Noweg, 2016).

Discovering a potential drug from a plant is a long, tedious, time-consuming and expensive venture, requiring the combined efforts of various expertise and sophisticated instruments in order to introduce the therapeutic chemical agents from the plants to mass market (Cordell, 1995). The programme would start with the fundamental study of preliminary pharmacological screening of the plants' extracts and upon significantly positive indication, isolation and elucidation of active compounds would proceed. At this point, the aims would diversify into;

(1) Isolating bioactive compounds to be used directly as drugs, for example morphine;
(2) Producing bioactive compounds of novel or known structures as lead compounds for semisynthesis, which will transform the toxic bioactive compounds to become patentable drugs of higher activity and/or lower toxicity, for example metformin, which are based, on galegine;
(3) Using agents as pharmacologic tools, and
(4) Using the whole plant or part of it as a herbal remedy, e.g., cranberry, echinacea, feverfew, garlic, ginkgo biloba, St. John’s wort, saw palmetto (Fabricant & Farnsworth, 2001; Taylor, Rabe, Mcgaw, Jäger, & Staden, 2001).

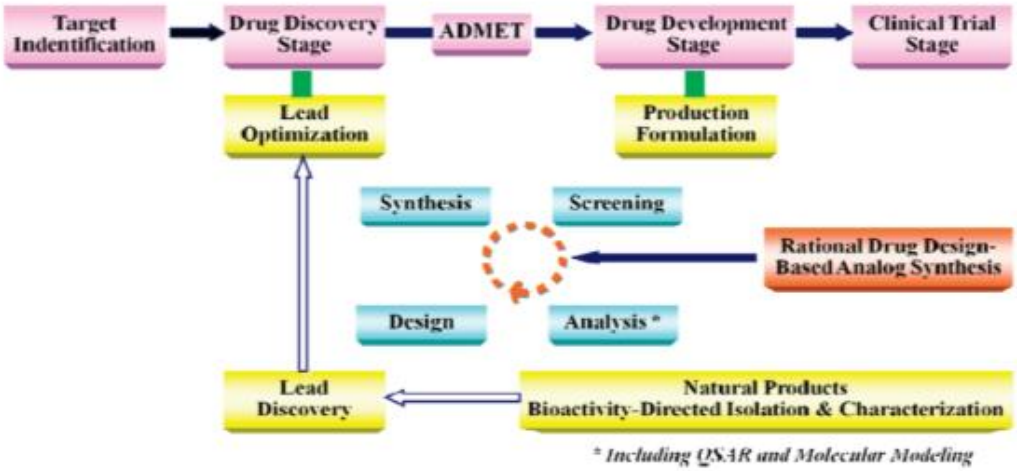

Figure 1: Flowchart of Natural Products-Derived Drug Discovery & Development Programme (Lee, 2010)

However, before any preliminary screening can be initiated, plants of interest should be identified. There are four approaches to drug discovery using plants; random selection followed by chemical screening, random selection followed by one or more biological assays, follow-up of biological activity reports, and follow-up of ethnomedical (traditional medicine) uses of plants, where leading information are searched in several sources; traditional medical systems (TCM, Ayurveda etc.), established databases such as NAPRALERT, and other approaches, for example by the plants' Latin binomials which indicates certain plants' characteristics like sweetness.

Based on several reviews (Balunas & Kinghorn, 2005; Butler, 2004), the traditional medicine approach in combination with bioactivity-directed isolation has been considered efficient and systematic, producing early drugs such as aspirin (**1**), digitoxin (**2**), morphine (**3**), quinine (**4**) and pilocarpine (**5**) (Figure 2). Among the FDA-approved drugs, 119 were found to be derived from traditional medicinal plants (Farnsworth, Akerele, Bingel, Soejarto, & Guo, 1985).

2.1. *Traditional Medicine, Medicinal Plants, Plant Chemistry: The Scientific Correlation*

The world's authority on health issues, World Health Organisation (WHO) has finally made a stand when it recognised Traditional Medicine (TM). TM, or else known as indigenous medicine or folk medicine, or in other terms as Complementary or Alternative Medicine (CAM), is in short, knowledge collections in regard to health maintenance and treatment developed over time by folks. By WHO definition, TM is:

" *the sum total of the knowledge, skills and practices based on the theories, beliefs and experiences indigenous to different cultures, whether explicable or not, used in the maintenance of health, as well as in the prevention, diagnosis, improvement or treatment of physical and mental illnesses*"

(WHO, 2000).

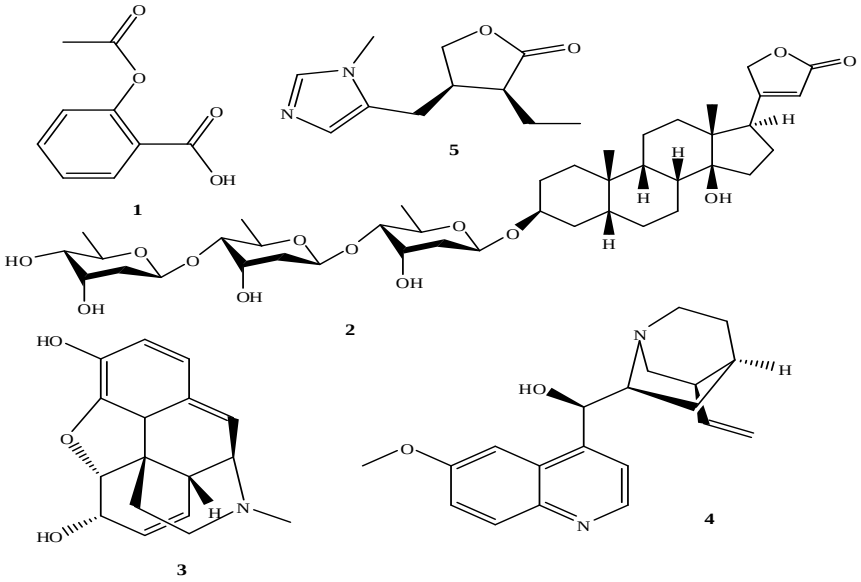

Figure 2: Drugs that were derived from traditional medicinal plants

The popularity of TM is worldwide, and for the last few decades is fast becoming an economic importance. If at the beginning of time, the use of TM is a matter of practicality and survival, today, it is rapidly gaining recognition due to its accessibility and affordability. In addition to the other mentioned fact, it is also deemed safe and effective . In developing countries, TM is very much depended on in terms of health care needs. 80% of the population in many Asian and African countries is using TM in some way or another. However, a growing trend of TM dependence has been detected in many developed countries like Australia, Canada and U.S. of America This is due to concern arising of adverse effects of chemical drugs as well as greater access to information (World Health Organization, 2019). In 2004, WHO reported that Herbal Medicine (HM) is a thriving business, becoming the most popular option in TM with a market value of USD60 billion annually. Apparently, an increasing trend in the trade of herbal health products all over the world (Fleck, 2004).

TM encompasses of systems; Traditional Chinese Medicine (TCM) which previously internationally known as acupuncture, Indian Traditional Medicine or more famously known as Ayurveda, Arabian's Unani, and other less known practices such as African TM, which is probably the oldest practice known to Man, Japanese Kampo, Indonesian *Jamu* and Malay, Thai, Aborigine, American and European TM (Janzen & Green, 2003; Ramawat, Dass, & Mathur, 2009). It has a long historical use of various applications passed on from generation to generation and demonstrated its safety and efficacy.

In the ancient period, by virtue of curiosity, Man had perhaps learnt to use plants, animals and minerals for treatment of illnesses and diseases, domestic and agriculture besides various

other applications, in combination of spiritual beliefs in addition to manual exercises by trial and error. These applications were taught by oral practice to the next generations by the elders for the survival of their kinds (Nuddin, 2016). Thus, when proper documentation was possible, writings which described the use of plants were found in these old civilisations as records of knowledge. The oldest record of such documentation is Mesopotamian clay tablets in cuneiform writing dated 2,600 year-old which mentioned the use of oils from *Cedrus*, *Cupressus* and a few other species to cure coughs, colds and other ailments. The same use of plants has been put into practice until today (Gurib-Fakim, 2006).

A medicinal plant is purported to possess curative property. In a WHO guideline, a medicinal plant is defined as, 'a plant which has been used for medical purposes at one time or another, and which, although not necessarily a product or available for marketing, is the original material of herbal medicines' (WHO, 2013). However, a discussion by G. A. Cordell & Colvard (2012) has put forth another way of defining medicinal plant. They emphasise the importance of validating the identity of a medicinal plant in terms of its botanical, chemical and biological virtues. In this modern, highly informative and sophisticated scientific technology world, a study of a medicinal plant in validating its curative property involves terms that do not exist 250 years ago, hence the need for a new meaning and approach. Scientifically, plants which exhibit potent biological effects on other organisms are said to possess strong biologically active secondary metabolites.

2.2 *Biologically Active Plant Secondary Metabolites*

In general, natural products are materials of natural origins either from human, plants, animals, insects and microorganisms. In a plant's cell, these natural products are produced by a metabolic system which provides two types of metabolites; primary and secondary metabolites, that are also referred to as natural products.

The primary metabolites are biological compounds produces by the process of photosynthesis, biochemically-controlled reactions which provide living organisms energy to live and tissues to grow and reproduce. They occur in all cells and play a central role in the metabolism and reproduction of those cells. These compounds are carbohydrates, lipids and proteins, which include the nucleic acids and the common amino acid. In primary metabolism, energy is produced via degradation of carbohydrates and sugars and oxidation of fatty acids from fats, while protein would be synthesised from interconversion of amino acids acquired from external and internal sources.

Secondary metabolites are products of intermediary metabolism, essentials that increase their overall ability to survive by overcoming local challenges. Secondary metabolism started by veering off from the main pathway, where biosynthesised intermediates are uniquely expressed in individual organism. Thus, secondary metabolites have limited distribution with specific roles in the species. They may be part of the defence system or in communication but often their functions are vaguely interpreted. Some of the roles of these very important secondary metabolites are straightforward; for instance, they play a host of general, protective roles (e.g. as antioxidant, free radical-scavenging, UV light-absorbing, and antiproliferative agents) and defend the plant against microorganisms such as bacteria, fungi, and viruses. In plants, secondary metabolites mainly function as chemical defensive agents which had evolved effectively for them to survive. They could be bitter in taste so that they would not be edible, for example alkaloids and terpenoids, or in colours as attractants in communication or camouflage, for example flavonoids and many more (Bhat, Nagasampagi, & Sivakumar, 2005; Kennedy & Wightman, 2011; Hanson, 2003; Ramawat et al., 2009).

There are more than 200,000 plant secondary metabolites, which have been vigorously studied by the scientists of various disciplines, from botany, chemistry, pharmacology, biochemistry, pharmacy, medicine and very recently, nanotechnology (Atanasov, Zotchev, Dirsch, Taskforce, & Supuran, 2021). Through collaborative efforts, studies such as chemotaxonomy, phytochemistry, drug discovery, drug delivery and many more flourish (Cordell, 1995). Natural products provide insights for biological markers in determining botanical and evolutionary relationships among species, drug leads in developing drugs, and mode of actions in understanding the biological activities (Cordell & Colvard, 2012). Natural products are very diverse, however, classifiable according to their parent chemical structure make-ups which arise from their particular biological synthesis (Hanson, 2003). The classes are:

(1) Polyketides and fatty acids, which are found in bacteria, fungi, plants and animals. They are formed by the stepwise condensation of acetate (ethanoate) units, resulting in a linear carbon chain derived from the 'building block' acetyl co-enzyme A. As the name suggests, they originated from poly-β-keto chains. Members of this class are fatty acids, polyacetylenes, prostaglandins, macrolide antibiotics and some aromatic compounds such as anthraquinones and tetracyclines (Dewick, 2001). The compounds had been reported to possess antimicrobial, immunosuppressant and antiparasitic activities, and are now in commercialisation (Hranueli et al., 2001).

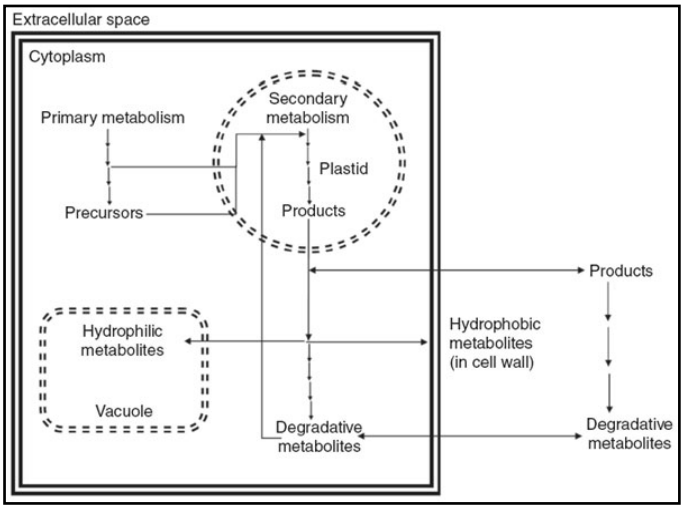

Figure 3:Sketch of plant cellular metabolism (Roberts, 2007)

(2) Terpenes and steroids, which are formed by assemblies of *iso*prene C_5 units, deriving from *iso*pentenyl (3-methylbut-3-en-1-yl) pyrophosphate and linked together in a head-to-tail manner, often in a characteristic branch structure. The sub-classes of terpenes are determined by the number of *iso*prenoids link in the carbon skeleton; Hemi-(C_5), Mono-(C_{10}), Sesqui-(C_{15}), Di-(C_{20}), Sester-(C_{25}), Tri-(C_{30}), Tetra-(C_{40}), Poly-terpene for $(C_5)_n$. This class of secondary metabolites is large and diverse, very often strong smelling for protective and/or communication purposes. Eventhough terpenes are plant-oriented secondary metabolites, they are important building blocks

for every living organism, for instance steroids is a sub-class of triterpene squalene (Breitmaier, 2006).

(3) Phenylpropanoids or sometimes known as phenolics, are compounds synthesised by plants which contained phenylpropanoid (C_6-C_3) units due to the starting material, amino acid phenylalanine. These compounds are part of plants' defence and communication systems, therefore, they are commonly found throughout the plant kingdom. Secondary metabolites belonging to this class of natural products are flavonoids, coumarins, stibenes, catechin, lignans and a few others (Vogt, 2010).

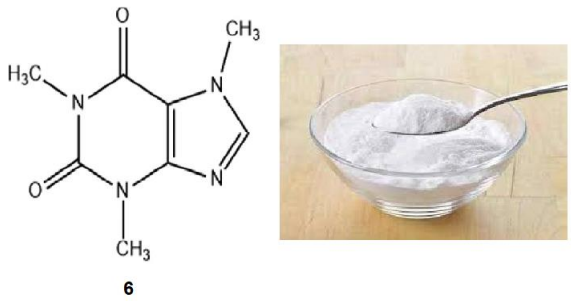

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Plate 2: White crystalline caffeine of coffee (Public domain image).

(4) Alkaloids, are structurally diverse chemical compounds with nitrogen atoms, derived from amino acids which mostly exist naturally as salts of organic acids in plants. They are classified according to their structural ring containing nitrogen, for example indole, thus reflecting their biosynthetic route. A secondary metabolite is considered an alkaloid when it is a cyclic organic compound containing nitrogen in a negative state which is of limited distribution among living organisms, as Pelletier described it in 1982 (M. F. Roberts & Wink, 1998). Among famous alkaloids which are consumed worldwide, are morphine (**3**) of poppy and caffeine (**6**) of coffee.

3. Aligning Strategic Research Agenda with Sustainable Development Goals

Borneo is the third largest island in the world at a land area of 743,330 square kilometres and home to one of the oldest rainforests in the world. It has a population of 21.3 million, living mostly at the coastal city areas and sparsely along the riverine. The island comprises of Malaysian Sabah and Sarawak, with Brunei squeeze between them and Kalimantan at its south. It consists of the Sabah's indigenous groups such as Dusun, Murut, Bajau etc., the Sarawakian's Dayak, Orang Ulu, Iban and so on, and the Indonesia's Banjar, Javanese, in addition to the other main ethnicities that are, Malay, Chinese and Indians (Marchetti, 1998). It is only logical that the various ethnic communities practise traditional cures and medicines through use of plants before the introduction of modern medical systems (Ahmad & Holdsworth, 2003).

In 2018, WHO released a report on non-communicable diseases for Malaysia, which estimated that 74% from total death causes were due to NCD (WHO, 2018). According to Malaysia's National Health and Morbidity Survey of 2019, the overall prevalence for diabetes among adults has an upward trend, from 11.2% in 2011, to 13.4% in 2015 and 18.3% in 2019 . On the other hand, overall prevalence for hypertension and hypercholesterolemia among adults has plateaued and declined respectively, from 2011 to 2019. Notably worrisome fact is

that 94.9% of the adults do not follow the recommended dietary intake of fruits and vegetable (IKU, 2019).

In the 20th century, the evolvement of food science began with scientific activities in identification of essential food elements to defining their roles in human health to linking diseases of public concern due to excessive intake of certain food components. All these reports led to increased public awareness on the importance of acquiring a diet that is low in saturated fat, and high in vegetables, fruits, whole grains and legumes to reduce the risk of chronic diseases such as heart disease, cancer, osteoporosis, diabetes and stroke (Hasler, 2002).

The scientific concept of 'functional foods' crystallised out of public need to understand the impact of food science through pharmacological aspect. As early as the Greek Era, food had been considered having medicinal values. As time progresses along with current technology, much has been studied and signified by various research groups and countries to determine rationale of functional foods. Thus, at the 10th International Conference in Santa Barbara in 2012, Functional Foods Centre, proposed a definition for "functional food":

"Natural or processed foods that contains known or unknown biologically-active compounds; which in defined amounts provide a clinically proven and documented health benefit for the prevention, management, or treatment of chronic disease."
(Martirosyan & Singh, 2015)

The SIG of CRBio has been actively studying traditional plants of Sabah with the intention to provide chemical and biological properties information of the plants from Borneo. We had started off by documenting traditional plants used by the Orang Sungai of Kinabatangan River, Sandakan (Nuddin & Ahmad, 2007) and carried out preliminary studies of certain functional foods that was *Tuhau*. The plant often consumed as pickle is likely to possess potent biological activities (Martang, Majitol, Jasnie, & Chor-Wai, 2020; Said, Tajudin, Mawah, & Nuddin, 2008; Tajudin, Said, Mawah, & Nuddin, 2008). The group had also performed a detailed study on the medicinal plant of Dusun known as *Pokok Manunggal*, or scientifically known as as *Quassia borneensis.* This plant is traditionally used to cure malaria. In the vitro study, it is found that the quassinoids and canthin-6-ones of *Q. borneensis* are susceptible to HL-60 leukemic cancer cell line and effectively inhibit the human erythrocytes infected with Chloroquine-Resistant *Plasmodium berghei* NK65 (Ghazali, Nuddin, Sabireen, Razali, & Ishak, 2013; Kamarulzaman, Ghazali, & Nuddin, 2015; Li, Ghazali, Razali, & Nuddin, 2015; Nuddin, Adam, & Hamzah, 2012; Wan Razali, Nuddin, Ishak, & Ghazali, 2015).

The aim of the research program is in accordance with the international's and national's policies. In the 17 *Sustainable Development Goals* (*SDGs*) (UN, 2015), the study fits the activities in the action plan for SDG 2 which aims to end hunger, achieve food security and improved nutrition and promote sustainable agriculture. The aim of the study also echoes Malaysia's *Dasar Agromakanan Negara* (DAN 2011-2020) in *Pendekatan* 2 & 7 which strives to develop high-valued agriculture through research and development (MoA, 2011). Additionally, the study also matches activities in the action plan for another important SDG, that is SDG 3, which is to ensure healthy lives and promote well-being for all at all ages. This plan resonates with our National Plan of Action for Nutrition of Malaysia III (NPANM III), 2016-2025, under MoH, Malaysia (MoH, 2016). One of the Facilitating Strategies is to strengthen Food and Nutrition Research and Development as it is deemed important to provide evidence for development of policies and programmes.

4. Conclusion

Nature provides diverse resources: the greens, the soils, the waters, the air and the fire. Therefore, very often human turn to Nature to fulfil their needs. They have experimented with plants and found them to be very beneficial. Much has been planned for the development of phytochemistry, otherwise known as natural products. In Malaysia, it has been progressing well from the early pioneers in the early 1980s, surveying plants through bioprospecting or ethnobotanical reports to compiling new secondary metabolites from various plant families and establishing their potent biological activities so that candidates for drugs can be found. Since then, a lot of missed shots, nevertheless, some close hits like Tongkat Ali, Kacip Fatimah, Misai Kucing, Hempedu Bumi and Dukung Anak. These plants were recognised as the main herbs to be focused in improving products quality and marketing efforts of dietary and herbal supplements as identified by Entry Point Project (EPP1) in Malaysian Agriculture Key Economic Area (NKEA) established in 2010.

Even in this age of modern technology, the use of traditional plants has been the key for the survival of the ethnic groups who live in the interior. In Borneo, rural folks who live far from towns and in forests still rely on traditional cures handed down to them through the generations. They use these plants in one form or another to cure illnesses (Kulip, 1997). The achievement of the biologically active medicinal plants study would highlight the potentials of traditional plants from Borneo to be recognised as functional plants providing beneficial nutrients for therapeutic purposes or health maintenance. The recognition would increase the visibility and popularity of the plants not just for personal consumption but public as well. Furthermore, the plants may be considered for crop development and becoming commodities. In addition, they may provide solution for innovation such as in flavour & aroma or nutraceutical industry.

Malaysia, and Borneo in particular, has a lot to offer. In terms of its biodiversity, it should not be confined to ecotourism. The richness of its resources should and could be explored, in a sustainable way for the benefit of the *rakyat*.

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