Germinated Brown Rice and Bioactive Rich Fractions:
On GOING JOURNEY FROM R&D TO COMMERCIALISATION

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Professor Dr. Maznah Ismail

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Contents

ABSTRACT

Over the past few decades, research has indicated a strong relation between nutrition and health. Recent advances in molecular medicine combined with the wealth of information generated by the Human Genome Project have fostered the emergence of nutrigenomics, a powerful new discovery tool that investigates the effects of nutrients and dietary ingredients on gene expression. Nutrigenomics may provide the strategies for the development of safe and effective dietary interventions against chronic diseases such as cardiovascular diseases, cancers, diabetes, Alzheimer's disease and the obesity epidemic. The increasing realisation that diet interacts with our genome at different levels, to induce changes towards health improvement and disease prevention, has been driving the search for functional foods and bioactive compounds or collectively known as nutraceuticals that promote health. My research has focused on finding those local foods and plant bioresources that can be used to improve the health of Malaysians and world community at large and to unravel their nutrigenomic mechanisms for successful interventions. Since rice is the staple of Malaysians and half of the world population, search on new rice types that can impart health benefits has been one of our research focus. These include work on germinated brown rice which was funded by Bernas and a new specialty high amylose rice partially funded by The World Academy of Sciences (TWAS) both of which have been found to have anti-diabetic property.

The desire to maximise the potentials of phytochemicals and food bioactives has led our team to develop "bioactive rich fractions" in which extracts contain multiple bioactive compounds, but with elevated levels of the selected primary or lead compounds. Our bioactive rich fractions have generally proven more effective than single bioactive compounds or even pharmaceutical agents.

Moreover, the use of supercritical fluid extraction system as a promising green technology has enabled the extraction and fractionation of bioactive rich fractions. The presence of the multiple bioactive compounds ensures food synergy, in which different bioactives act synergistically to produce superior functional effects in comparison with single bioactive compound or even drugs. Although rich fractions effectively increase the bioactivity of the extract or food, the standardisation and quality assurance process can be challenging, and much of our research is currently focused on these areas. My work on bioactive-rich fractions has contributed in no small measure in advancing the fields of nutraceuticals and nutrigenomics. Furthermore, several successes have been achieved in the field of nanotechnology for the pharmaceutical industry, which has recently been extended to nutraceuticals and functional foods industry. Our experience with nanonisation of nutraceuticals is so far promising in enhancing the bioactivity of nutraceuticals through increased duodenal absorption or tissue uptake and reducing their side effects profile. Despite the successes recorded thus far, commercialising research outputs into commercial products has been challenging. Nevertheless with the strong support from the University and my research team, we have managed to commercialise two nutraceutical products through the setting up of two start-up companies namely Nutracreme Sdn Bhd and Orygold Sdn Bhd in the hope that this will bring benefits to the general populace for better quality of life.

Keywords: *nutrigenomics, nutraceuticals, commercialisation, functional food, germinated brown rice, bioactive rich fraction, nanotechnology.*

INTRODUCTION

The desire to improve health and prevent diseases continues to drive the search for newer therapies. Interest in the medicinal properties of natural products has grown considerably due to concerns about side effects and other adverse effects caused by synthetic compounds. Furthermore, for a given disease condition, multiple drugs are often being prescribed since each drug consist of a single compound which acts on a specific pathway. Such interest has yielded a better understanding of the role of nutraceuticals in health promotion and disease prevention, and their functional potentials are currently the subject of close scrutiny (Briskin, 2000; Gurib-Fakim, 2006). Diseases have always been a part of human existence, and so has the search for remedies, not only to restore health, but more importantly to improve the quality of life. For centuries, people have realised that dietary components can promote health and alleviate diseases, as observed by Hippocrates' 'Let food be thy medicine and medicine be thy food'. In recent years, this realisation has resurfaced and has been supported by evidence-based studies that show a direct link between diet and the development of chronic disease. Chronic diseases have been known as the leading causes of death in developed countries, and, even in developing countries, with an epidemiologic transition reflecting a changing pattern of morbidity and mortality from predominantly infectious aetiologies to chronic diseases (WHO, 2008). The unbearable effects of chronic diseases, even when they do not lead to death, have significant impacts on individuals, their families and the economies of nations. Improvements in health can therefore have far-reaching benefits. Given this dismal picture and the high cost of managing these diseases, preventive strategies have been given a priority, and genuine advances in managing chronic diseases have been reported, though on a limited scale.

These emerging patterns of diet–disease interactions have led to more in-depth studies of dietary components, especially in the form of plant bioactives and their health benefits. In addition, the need to reduce the cost of managing chronic diseases, especially in developing countries, has given more impetus to research in this field to provide chronic disease remedies from natural sources, which are abundantly available in many of these countries (Hoareau and DaSilva, 1999). However, this approach may have disadvantages, given that plants play a crucial role in maintaining a balanced ecosystem. Unlike the simplistic view, which suggests that only a thin line exists between health and disease, a more encompassing approach to health management must be taken to cover the multiple 'grey areas' that exist between the two states of wellbeing. These 'grey areas' must consider anything that has an impact on disease and/or health. This consideration has brought forth concepts that now try to minimise the adverse impact of human activities on the environment, relating to the processes of planting, harvesting, processing or developing any agricultural product with health benefits. As such, advances in technology have ensured that adverse environmental effects due to the utilisation of plants for their health benefits are minimised.

Similarly, important advances have been recorded in the area of nutritional sciences. Nutrition research previously focused on the deficiency states of major food macromolecules, but its focus has changed over the last decade due to an increasing awareness of the interaction of food and its constituents with macromolecules at different molecular levels. This is largely what has given birth to the field of nutrigenomics, which focuses on the interactions at the diet–genome interface (Gillies, 2003; Kaput and Rodriguez, 2004; Mutch *et al*., 2005; Afman and Muller, 2006). It is through these interactions that plant and food bioactive compounds are believed

to influence the molecular and biochemical processes in biological systems (Muller and Kersten, 2003). Specifically, in nutrigenomics, the particular focus is on understanding the molecular relationships between nutrition and the response of genes and how such changes can affect human health (Afman and Muller, 2006; Subbiah, 2007). Advanced molecular biology tools and the mapping of the entire human genome make these studies possible within a considerably shorter amount of time than previously anticipated through the use of high-throughput genomic tools that generate data within a very short time. The basis for nutrigenomic studies is that dietary components act as signals that convey information about the diet and its components to cells or subcellular components in biological systems. These dietary components are then detected by sensor systems in the cell at different levels (genome, epigenome, proteome and metabolome) to change gene and protein expression and metabolite production in accordance with the level of nutrients sensed by the cell. Dietary signatures are thought to underlie the health benefits of plant bioactive compounds, commonly referred to as nutraceuticals (Kauwell, 2005; Afman and Muller, 2006; Subbiah, 2007). The word 'nutraceutical' was coined in 1989 by Dr Stephen DeFelice (Hardy, 2000; Kalra, 2003) and refers to foods or parts of foods that provide medical or health benefits, including the prevention and/or treatment of disease beyond nutritional needs (Hardy, 2000).

Our team has been working on nutraceutical development for more than two decades looking for new sources, medical applications and their nutrigenomic actions. Several plants and foods have traditionally been consumed for medicinal purposes throughout human history. In recent years, studies have revealed many phytochemicals and food bioactives exhibit pharmacological properties (Edeoga *et al.*, 2005; Iwu, 2014; Van Wyk and Wink,

2004). The desire to maximise the potentials of these bioactives has led our team to develop "bioactive rich fractions" and functional foods, in which the primary compound is synergistically potentiated by smaller amounts of other bioactive compounds (Imam *et al.,* 2015). The concept of bioactive-rich fractions and functional food is largely based on food synergy (Jacobs *et al*., 2009; Jacobs and Tapsell, 2007), in which whole food due to the presence of multiple bioactives and not any single nutrients is considered the fundamental unit of nutrition. Through the synergy of bioactive compounds in foods and plants, more nutritive value is derived compared with individual nutrients. Because the various compounds are derived from a single source, a better functional effect is attained.

Furthermore, over the years, the role of staple foods in providing adequate nutrition has been acknowledged. Historically, the choice of staple foods used to be based on availability, proximity to communities, and palatability. The health benefits were never considered in such choices. Even when scientific advances set in, it took many decades for the focus of staple foods to shift towards purely health benefits (Kuhnlein and Receveur, 1996; Kearney, 2010; Weststrate *et al*., 2002). Admittedly, nutrition research focused, in much of the earlier part of the 20th century, on functions of the major macromolecules (carbs, proteins and fats) and their deficiency states and how those could be managed. In the later part of the 20th century, focus shifted towards provision of staple foods with enhanced health benefits (Weststrate *et al*., 2006; Vergères, 2013; Graham *et al*, 1999; DellaPenna, 1999; Nestel *et al.*, 2006). Iron, vitamin A, minerals and nutraceuticals were fortified in staple diets this way (Stoltzfus and Dreyfuss, 1998; Drewnowski, 2005; WHO/UNICEF/IVACG, 1997; Tontisirin *et al*., 2002).

NUTRIGENOMIC MANAGEMENT OF CHRONIC DISEASES

Advances in nutrition research, especially in the post-human genome era, have resulted in the evolution of newer fields of nutrition research. With this came the realisation that diets were important variables in the causation of disease and health maintenance (WHO/FAO, 2002; Carrera-Bastos *et al*., 2011); diets have the capacity to interact with the human genome at different levels, and could result in changes in the transcriptome, proteome and metabolome (Afman and Müller, 2006; Müller and Kersten, 2003; Mutch *et al*., 2005). These interactions at the diet-genome interface have tremendously advanced our understanding of the roles played by diets in health and disease (Figure 1).

Dietary signals elicit changes in transcriptional factors following interactions with receptors resulting in transcriptional (transcriptomics) and translational (proteomics) changes that affect metabolic content of cells (metabolomics) in different ways. When the resulting changes produce favorable metabolic outcomes, disease prevention and health promotion are the end result (Müller and Kersten, 2003). Nutrigenomics has recently been the focus of much attention within the nutritional sciences, in an attempt to understand the role of diets in regulation of the genome, and what type of diets and dietary components could be used to improve health. Studies in this area have given birth to the understanding that environmental factors especially dietary not only regulate the genome in those that directly experience them but also across generations (Mathers *et al*., 2009; Feil, 2006; Skinner *et al*., 2010).

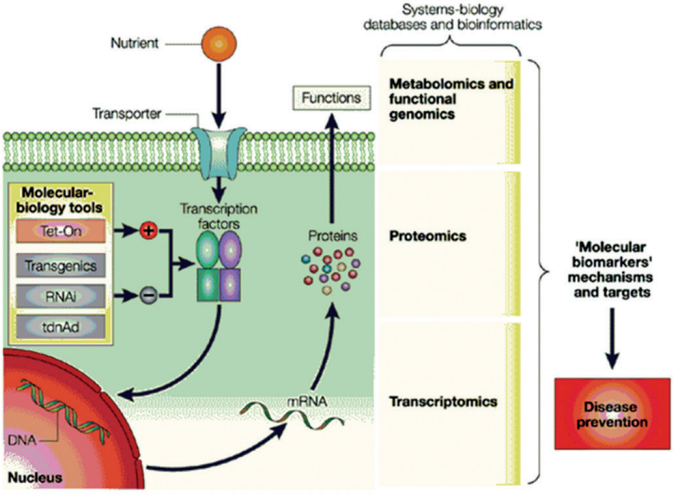

Figure 1 Schema showing nutrigenomic tools used to study nutrient-gene interactions and disease mechanisms. Nutrient sensing by cells can lead to changes in expression of genes, mostly mediated by transcriptional factors, with changes in levels of mRNA (transcriptomics), proteins (proteomics) and metabolic contents (metabolomics). Use of molecular biology tools to modulate the nutrient sensing of cells can add to understanding on bioactivity. Overall, nutrigenomic studies increase understanding on molecular markers influenced by nutrients and targets for disease prevention and health promotion.
(*Source:* Müller amd Kersten, 2003)

Such transgenerational studies are thought to be the underlying reason for some hitherto considered evolutionary changes observed in humans across generations. Furthermore, the genetic basis of most diseases is now believed to have epigenetic links due to the environmental factors. As such, observational studies and genome-wide association studies have indicated that only about 10% of chronic diseases can be explained by genetic susceptibility and that over 90% of cases are traceable to environment especially dietary factors (Whitehead and Whitehead, 1999).

Obesity, metabolic syndrome, cancers, type 2 diabetes and other chronic diseases have been on the increase despite advances in healthcare delivery and management of these diseases (Strong *et al*., 2005; Mathers and Loncar, 2006). It is likely that dietary and other environmental factors are contributing to such increases in disease incidents across generations (Mathers *et al*., 2009; Feil, 2006; Skinner *et al*., 2010). As more studies unravel these hypotheses, it remains to be speculated that dietary factors especially staple diets may have a huge role in such disease incidents. Considerations of the role of diet in causation of chronic diseases, its potential for disease prevention, and finally the transgenerational implications of diets, dietary components and dietary habits underline diet as an important variable in the overall global burden of diseases. This is more so when diets are consumed in the form of staple foods; the continuous nature of consumption of staple foods on a daily basis means the components of such diets will impact on the health of individuals continuously over long term. Therefore, this calls for action on choice of staple diets that not only improve health of individuals but also could improve health across generations through epigenetic modifications. The enormous consumption of rice across much of Asia and Africa suggests that it is a staple food that deserves considerable attention in order to safeguard the health of over half the world's population, who often times consume this staple because of availability and affordability (Khush, 2005). In this regard, the health implications of the commonly consumed rice (polished rice) have received considerable attention, although the outcome does not inspire as much confidence. This has prompted calls for better alternatives.

Already, it is documented that chronic diet-related diseases are the leading cause of death globally, with huge burden on much of Asia and Africa, where there are limited resources to provide

state-of-the-art healthcare facilities (Yach *et al*, 2004; Abegunde *et al*., 2007). With the threat of food security in many parts of the developing world, stakeholders are championing a cause for more food availability and sustainability in feeding the world's population. Not only should these agencies support the provision of any food, they should in addition support the provision of healthy foods to avert moving from one crisis (hunger) to another (metabolic diseases). This is very important for the poor developing countries where white rice is the main staple food, which of recent has been linked to development of chronic disease like type 2 diabetes and its complications (Sun *et al*., 2010; Hu *et al*., 2012; Nanri *et al*., 2010).

HEALTH IMPLICATIONS OF RICE CONSUMPTION: OUR CONTRIBUTIONS

As can be recalled, white rice is a major staple food for people in low to middle income countries and recently it has been linked to the development of type 2 diabetes. The incidence and prevalence of type 2 diabetes in those countries is projected to increase (International Diabetes Federation, 2013), and though a direct link has not been made, excessive white rice consumption may be contributing to the growing trend. In fact, despite the evidence linking white rice to diabetes, Kadoch believes it may not be a direct link and that adoption of western lifestyle is largely to blame for the burden of diabetes (Kadoch, 2012). In a review, Hu argued that multiple factors are responsible for the growing incidence and prevalence of diabetes in Asian countries (Hu, 2011). However, it is also possible that excessive white rice consumption is contributing to some extent in view of recent evidence linking it to diabetes and its daily and enormous consumption in Asian countries.

Sun *et al.* (2010) reported an increased risk of diabetes among white rice consumers, and that replacing one-third of daily serving with brown rice will reduce the risk of developing type 2 diabetes. Nanri *et al.* (2010) also reported an increased risk of type 2 diabetes in women who consumed white rice, although Zhang *et al.* (2011) reported not finding a similar association in middle aged Chinese men and women. A meta-analysis involving over 350,000 subjects followed up for 4-22 years, however, showed an increased risk of type 2 diabetes among Asians who consumed white rice instead of brown rice (Hu *et al*., 2012). It still remains controversial, however, especially since Kempner had used white rice to manage cardiometabolic diseases (Kempner *et al*., 1958; Nuttall, 1983). Interestingly, fruits and vegetables were included as part of the diet, and they may have cancelled out any negative effects of white rice (Liu, 2003). High glycemic index of white rice is likely the reason behind the worsening of cardiometabolic risks due to its consumption (Miller *et al*., 1992; Jenkins *et al*., 2002; Barclay *et al*., 2008). High glycemic index will promote postprandial hyperglycemia, glucose-induced oxidative stress and eventually cardiometabolic risk (Rebolledo and Dato, 2005; Ludwig, 2002). The risks associated with white rice consumption based on the findings so far suggest that less consumption of white rice may be helpful towards reducing risk of cardiometabolic diseases especially type 2 diabetes. Furthermore, epigenetic studies have demonstrated that dietary factors and habits can induce intrauterine molecular reprogramming events in growing fetuses with consequent increase in the risk of chronic diseases (Mathers *et al*., 2009; Skinner *et al*., 2010). Hence, it is likely also that epigenetic events due to excessive white rice consumption are promoting the transgenerational risk of cardiometabolic diseases. Moreover, we have recently demonstrated that prenatal exposure of rats to white rice increases their risk of

metabolic perturbations and tend towards insulin resistance, while brown rice reduces such risks (Imam *et al*., 2015). The white rice-induced risk of insulin resistance in offsprings due to dietary exposures from their parents may require very little postnatal stimuli to develop overt type 2 diabetes. Thus, there is need for healthier alternatives for white rice in order to lower chronic diseases burden among white rice consuming countries.

Rice grown on the paddy usually has chaff (husk), which when dehulled yields the brown rice. Milling of brown rice to remove the outer bran layer and germ will then produce the white rice (mainly the endosperm) commonly consumed. The outer bran layer removed during milling contains bioactive compounds that have disease-preventing potentials (Figure 2) (Wu *et al*., 2013).

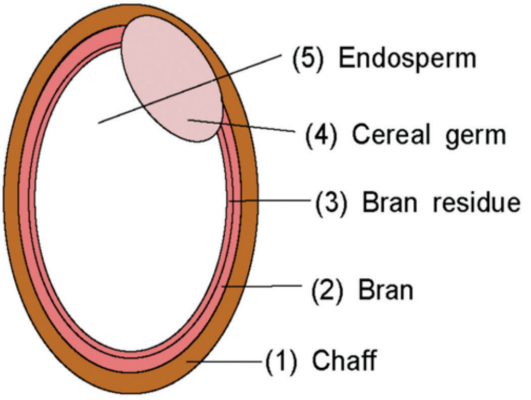

Figure 2 Schema of rice grain showing the various parts as it is derived from the paddy. The chaff is dehulled to access the bran layer, which is often removed together with the germ to get the white rice (mainly endosperm) that is commonly consumed.
(*Source*: Wikipedia)

Over 3 billion people are thought to be dependent on white rice as a staple food, especially in Asia and Africa where the burden of chronic disease is on the increase (Khush, 2005; Yach *et al*., 2004). Brown rice is not consumed as much as white rice partly due to its hard texture. This wholegrain food, however, has been reported to contain bioactives like γ-aminobutyric acid (GABA), γ-oryzanol, dietary fibre, acylated steryl glycoside (ASG), minerals and vitamins mostly in the bran layer (Table 1). To overcome the problem of hard texture and improve palatability, germination of the brown rice is commonly done (Wu *et al*., 2013; Imam *et al*., 2012). Germination entails soaking brown rice in water with/without the use of seed stressors like anoxia treatment, sodium hypochlorite and hydrogen peroxide (Wu *et al*., 2013; Ismail *et al*, 2014). The outcome of the germination process is a grain that is less hardy and more palatable. Interestingly, our experience has shown that during the process of germination, activation of hydrolytic enzymes, notably amylase, not only breaks down seed molecules like amylose that give the seed its lower texture, but also catalyses the production of more bioactive compounds in the seed (Wu *et al*., 2013; Imam *et al*., 2012). The increased bioactive composition of the germinated brown rice is a reflection of the increased demands for seed growth (Ismail *et al*., 2014). However, arresting the germination of the grain at the appropriate time (evidenced by appearance of sprouts, Figure 3) by removing optimal germination conditions maintains the high bioactive composition, which can be consumed for health benefits (Figure 4)

Table 1 Germinated brown rice bioactives and their potential bioactivities

Nutrients	Biological activities in germinated brown rice	Reference
Acylated steryl glycoside	Antioxidant Hypocholesterolemic Antihyperglycemic	Imam et al., 2012
GABA	Hypotensive effect Accelerating metabolism in brain, and preventing headaches or depressions after effects of cerebral arteriosclerosis and cerebral apoplexy. Preventing climacteric disorder. Preventing presenile derangement such as insomnia and mental irritation. Activating renal function	Patil & Khan, 2011
Dietary fiber	Relieving constipation. Preventing cancer of colon Regulating blood sugar levels	Patil & Khan, 2011
Inositols	Accelerating fat metabolism Preventing fatty liver Preventing arteriosclerosis	Patil & Khan, 2011
Ferulic acid and other phenolics	Antioxidant including scavenging super oxides Suppressing melanogenesis	Patil & Khan, 2011
Phytic acid	Antioxidative effect Preventing cardiovascular disease Preventing platelet aggregation	Patil & Khan, 2011

Nutrients	Biological activities in germinated brown rice	Reference
Tocotrienols	Scavenging super oxides Protecting skin from ultraviolet rays	Patil & Khan, 2011
Magnesium	Preventing heart diseases	Patil & Khan, 2011
Potassium	Lowering blood pressure	Patil & Khan, 2011
Zinc	Activating reproductive function Preventing arteriosclerosis	Patil & Khan, 2011
Gamma- oryzanol	Antioxidative effect Preventing skin aging Hypocholestrolemic	Patil & Khan, 2011
Prolylendopeptidase inhibitor	Preventing Alzheimer's disease	Patil & Khan, 2011

Figure 3 Photo of germinated brown rice. The sprouts indicating germination are indicated by dark rings. The sprouts appear when enough stimuli have been applied to induce germination of the seeds. The rice grains in the photo were germinated over 24 h, similar to what we reported in Ismail *et al*., 2014.

(Photo courtesy of Siti Farhana Fathy and Der-Jiun Ooi, Laboratory of Molecular Biomedicine, Institute of Bioscience, Universiti Putra Malaysia)

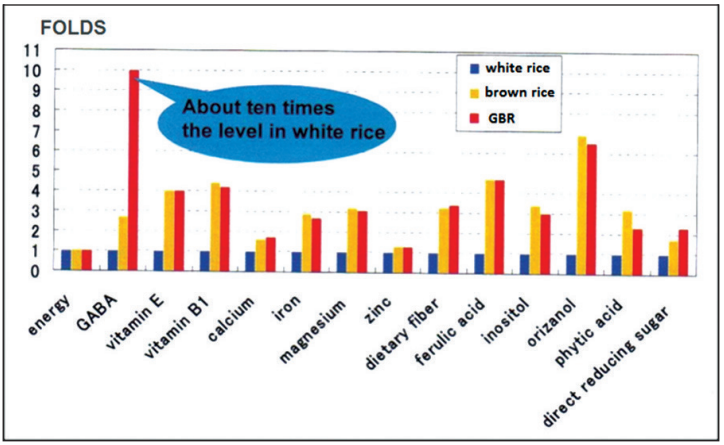

Figure 4: Numerous studies including those from our group have demonstrated the improved bioactive composition of brown rice following germination (Table 2). In fact, we have used a combination of three effective methods of germination and time dependant that yielded significantly high levels of bioactives (Ismail *et al*., 2014). In particular, a comparison of the GABA content of our germinated brown rice after 24 h of germination indicated that it was higher than what others reported for germination times of 48 and 72 h (Imam *et al*., 2013; Roohinejad *et al*., 2010). This improved bioactive composition is believed to be the reason behind the increased bioactivity of germinated brown rice compared to brown rice. Also, the improved texture of germinated brown rice over brown rice means it is likely to be patronised more than brown rice, and white rice for health reasons. Already, there have been reports that germinated brown rice incorporated into bread and other food products had good texture and was received positively than if brown rice was used (Imam *et al*., 2012; Kim, 2013).

Table 2 Changes in concentrations of bioactives during germination of brown rice grains

Bioactive	Changes during germination	Reference
Gamma aminobutyric acid (GABA)	↑ GABA	Imam *et al*., 2013; Komatsuzaki *et al*., 2007; Imam & Ismail, 2013
Dietary fiber (DF)	↑ DF, ↑ soluble fibre, ↓ insoluble fiber	Li *et al*., 2007; Banchuen *et al*., 2009; Maisont and Narkrugsa, 2010; Oh *et al*., 2010; Li *et al*., 2012; Lee *et al*., 2007; Jayadeep and Malleshi, 2011
Acylated steryl glycoside (ASG)	↑ ASG	Imam *et al*., 2013; Imam and Ismail, 2013; Usuki *et al*., 2008
Phenolics and antioxidants	↑ phenolics and antioxidant activity	Imam *et al*., 2013; Li *et al*., 2008; Maisont and Narkrugsa, 2010; Imam *et al*., 2012; Imam and Ismail, 2013; Tian *et al*., 2004; Sawaddiwong *et al*., 2008; Jongjareonrak *et al*., 2009; Kim *et al*., 2011; Azmi *et al*., 2013; Sani *et al*., 2012
Proteins	↑ proteins	Banchuen *et al*., 2009; Watchararparpaiboon *et al*., 2010; Lee *et al*., 2007; Moongngarm and Saetung, 2010

Bioactive	Changes during germination	Reference
Fats	↑ fat	Banchuen *et al*., 2009; Watchararparpaiboon *et al*., 2010; Lee *et al*., 2007
Vitamins	↑alpha-tocopherol, ↑alpha-tocotrienol, ↑gamma-oryzanol, ↓gamma-tocopherol, ↓gamma-tocotrienol, ↑ thiamine	Watchararparpaiboon *et al*., 2010; Jayadeep and Malleshi, 2011; Britz e*t al*., 2007
Gamma- oryzanol	↑ oryzanol	Imam *et al*., 2013; Oh *et al*., 2010; Imam and Ismail, 2013
Amylose content	↑free sugars, ↑amylose	Banchuen *et al*., 2009; Maisont and Narkrugsa, 2010; Li *et al*., 2012; Songtip *et al*., 2012; Lee *et al*., 2007; Jayadeep and Malleshi, 2011; Musa *et al*., 2011; Xu *et al*., 2012
Minerals	↑ magnesium and chloride	Ismail *et al*., 2014

↑=increased, ↑=decreased. Germination of brown rice to reduce its hard texture also potentiate the bioactive composition of the rice grains, and the higher amounts of bioactives is belived to confer germinated brown rice with its enhanced bioactivity.

Consumption of staple foods like germinated brown rice with potentially better health benefits due to higher amounts of bioactive compounds can be a way to provide continuous availability of health promoting bioactive compounds. It is also a convenient way to manage chronic diseases through daily diets. This is even more so for parts of the world where economic constraints make it difficult for individuals to have access to state-of-the-art healthcare facilities. Staple foods with functional properties will have more benefits to these people through health promotion and disease prevention, than any medication or treatment modality they cannot afford when they become ill.

The documented functional effects of germinated brown rice include antidiabetic, antioxidant, weight reducing, hypocholesterolemic, antidepressant, cognitive-enhancing, hepatoprotective and immunomodulatory properties (Wu *et al*., 2013; Imam *et al*., 2012, Pati and Khan, 2011). Considering these properties of germinated brown rice, it could potentially produce better outcomes especially for cardiometabolic diseases than pharmacological agents, which often have single pharmacological action and many side effects. Also, metabolic changes due to disease processes cause underlying associated transcriptional or translational perturbations, which may not be the target of most pharmacological agents. There are now more studies addressing these issues including nutrigenomic studies underlying the health benefits of germinated brown rice which have provided some mechanistic insights into its functional properties. Relevant studies are reviewed below (Table 3).

Table 3 Summary of Nutrigenomic mechanisms involved in GBR functional effects

Bioactivity	Underlying nutrigenomic mechanism	Reference
Antiobesity	Suppression of fatty acid synthesis and fat deposition in adipose tissues via transcriptional regulation of adipogenic (C/EBPα, PPARγ, and SREBP-1c), FAS, aP2, LPL and inflammatory (IL6 and TNF) genes	Ho et al., 2012; Ho et al., 2013; Imam et al., 2013
Hypocholesterolemia	Reduction in total cholesterol and LDL and increase in HDL via transcriptional regulation of hepatic LDLR, adiponectin, LPL, PPARγ, AKT and ABCA 1 and apolipoprotein A genes	Imam et al., 2013; Imam et al., 2014
Antihyperglycemia	Reduction in blood glucose through suppression of gluconeogenic (fbp and pck) genes	Imam & Ismail, 2013
Antioxidative	Increase in antioxidant status and reduced oxidative stress via transcriptional regulation of antioxidant (SOD, catalase and IGF2), and anti-apoptotic (AKT, NF-Kβ, ERK1/2, JNK, p53 tumor suppressor gene and p38 MAPK) genes	Imam et al., 2012; Azmi et al., 2013; Imam et al., 2012; Imam et al., 2012

Activity against menopause-related problems	Transcriptional regulation of bone metabolism genes, including BMP-2, SPARC, RUNX-2, Osx, periostin, Postn, Col1&2 and CGRP. Upregulation of uterine expression of estrogen related genes (ER-β, CaBP9k, C3, HSP70, and IL4 receptor)	Muhammad et al., 2013; Muhammad et al., 2013;

ABCA: ATP binding cassette; AKT: v-akt murine thymoma viral oncogene; aP2: adipocyte fatty acid-binding protein; BMP-2: bone morphogenic protein-2; C3: complement protein; CaBP9k: calcium-binding protein; CGRP: calcitonin receptor gene; Coll 1&2: collagen 1&2; C/EBPα: CCAAT/enhancer binding protein; ER-β: estrogen receptor-beta; ERK1/2: extracellular signal-regulated kinase 1/2; FAS: fatty acid synthase; HDL: high density lipoprotein; HSP70: heat shock protein 70 kDa; IL4: interleukin 4; IL6: interleukin 6; JNK: c-Jun N-terminal kinase; LDL: low density lipoprotein; LDLR: LDL receptor; LPL: lipoprotein lipase; NF-Kβ: nuclear factor beta; Osx: osteoblast-specific transcription factor osterix; p38 MAPK: mitogen activated protein kinase; Postn: osteoblast specific factor; PPARγ: peroxisome proliferator-activated receptor γ; RUNX-2: runt-related transcription factor 2; SPARC: secreted protein acidic and rich in cysteine; SREBP-1c: sterol regulatory element-binding protein-1c; SOD: superoxide dismutase.

GBR is an innovative rice as it has most, if not all nutrients, in addition to elevated bioactives in the rice grain for human consumption. The versatility of GBR use includes rice flour, food substitutes as well as food ingredients. It has been applied in many dishes throughout the world. Italian risotto, Spanish paella, Brazilian fejoada, and Indian curry with rice, etc. would be some of suitable examples for using GBR (Liu, 2003). Already, GBR is being used to make many food products such as rice-balls, soup, bread, doughnuts, cookies, rice burger and mixed with other ingredients (Liu, 2003). As such GBR could be well used as a tool to improve food security in regions facing food shortage. For developed and developing countries, GBR can be a dietary food for health improvement and hence its consumption deserves profound popularity throughout the world.

Nutrigenomic Effects of Germinated Brown Rice on Metabolic Indices Related to Diabetes and Cardiovascular Diseases (CVD)

CVDs remain the most significant cause of morbidity and mortality globally (Yach *et al*., 2004). There have been advances in the management of CVDs, but the growing burden of the disease has prompted search for better alternatives to currently available drugs. In fact, many of the drugs used in the management of CVD cause serious side effects (Bellosta *et al*., 2004). Close links have been unraveled between diet and the risk factors for CVD. Hence, dietary factors can promote cardiometabolic risk through hypercholesterolemia and increased oxidative stress, while diets with opposite effects will lower such risks (Mann, 2002). Germinated brown rice has been studied extensively for its cardioprotective effects, including its ability to reduce risk

factors like dyslipidemia, excess plasminogen activator inhibitor-1, oxidised low density lipoprotein (LDL), and hypertension, mediated through its bioactives (Wu *et al*., 2013; Imam *et al*., 2012). We have demonstrated that germinated brown rice lowered cholesterol and reduced the risk of CVD through regulation of hepatic cholesterol related genes including LDL receptor (LDLR), apolipoprotein A (APOA), adiponectin, lipoprotein lipase (LPL), peroxisome proliferator-activated receptor gamma (PPARγ), v-akt murine thymoma viral oncogene (Akt) and ATP-binding cassette (ABCA) 1 (Imam *et al*., 2013; Imam *et al*., 2014). Increased expression of hepatic APOA may underlie the increased high density lipoprotein (HDL) concentrations observed following germinated brown rice supplementation (Imam *et al*., 2013), while upregulation of hepatic adiponectin indicate an increased synthesis of adiponectin as the basis for the increased circulating adiponectin levels observed in rats (Torimitsu *et al*., 2010). Adiponectin is known to improve metabolic indices and reduce the risk of cardiometabolic disease and complications (Rabe *et al*, 2008; Declercq *et al*., 2013). Additionally, LDLR is responsible for cholesterol uptake and clearance by the liver, and hence its upregulation in the liver partly explains the lower LDL levels observed due to germinated brown rice (Imam *et al*., 2013). Also, upregulation of hepatic Akt, and downregulation of hepatic LPL and PPARγ are suggestive of cholesterol metabolism-enhancing abilities of germinated brown rice in the liver (Imam *et al*., 2014). These changes possibly explain the improved cholesterol metabolism, including lower levels of total cholesterol and LDL, and higher levels of HDL, seen when germinated brown rice is consumed. These multiple mechanisms of cholesterol regulation by germinated brown rice indicate how effective it could be towards reducing hypercholesterolemia and eventually CVD risk. Overall, these effects indicate a potent cardioprotective recipe.

Germinated brown rice has been reported severally to reduce weight, partly through promoting breakdown of fat as we have demonstrated and also through regulation of adipogenic genes (Imam and Ismail, 2013; Ho *et al*., 2012; Imam *et al*., 2014). Gluconeogenesis promotes breakdown of fat and protein sources for the production of glucose, and in diabetes, this process becomes hyperactive (Magnusson *et al*., 1992). Germinated brown rice was shown to suppress gluconeogenesis and reduce weight irrespective of its effect on gluconeogenesis likely by promoting breakdown of fat (Imam and Ismail, 2013). Conversely, Ho *et al*. have reported that adipogenic (CCAAT/enhancer binding protein [C/EBPα], PPARγ, and sterol regulatory element-binding protein-1c [SREBP-1c], fatty acid synthase [FAS], adipocyte fatty acid-binding protein [aP2], and LPL), and inflammatory genes (IL6 and TNF) are suppressed by germinated brown rice (Ho *et al*., 2012; Ho *et al*., 2013). Changes in the adipose tissue that promote build-up of fat deposits are closely linked with inflammation (Wellen and Hotamisligil, 2003), which germinated brown rice was shown to suppress and eventually reduce obesity. Overall, the findings so far suggest that GBR reduces weight through multiple transcriptional mechanisms that eventually promote fat catabolism and prevent fat deposition. Reduced rates of obesity are important among the low and middle income countries to lower risks of chronic disease, especially with sedentary lifestyles that promote cardiometabolic disease risks among these people becoming more common. In particular, risk of cardiometabolic disease is reported to be higher among Asian populations, where white rice is consumed enormously, even at lower body mass indices (Hu, 2011). Communicable diseases are still a problem and the rising burden of non-communicable diseases in these countries may be too much to bear. Germinated brown rice may be a healthier choice of staple for these countries.

Oxidative stress is implicated as an underlying factor in many chronic diseases and their complications (Aruoma, 1998). White rice promotes oxidative stress through glucose-induced toxic changes, while brown rice and germinated brown rice have antioxidative properties that are likely mediated through multiple mechanisms. High amounts of antioxidants including GABA, phenolics, ASG and vitamins may explain the potent antioxidative effects of germinated brown rice. Several studies have shown high antioxidant potentials for GBR extracts, which contribute towards its effects against lipid peroxidation and other oxidative changes (Imam *et al*., 2012). Usuki *et al.* (2011) demonstrated that germinated brown rice reduced oxidative stress in type 2 diabetes through induction of insulin-like growth factor 1. In addition, we have shown that upregulation of hepatic antioxidant genes including catalase and superoxide dismutase (SOD) by germinated brown rice bioactives may underlie its antioxidative effects (Imam *et al*., 2012; Imam *et al*., 2012; Imam *et al*., 2012). In particular, germinated brown rice was shown to upregulate SOD2, which is strongly associated with antioxidative and antiapoptotic effects (Kannan and Jain, 2000). Similarly, germinated brown rice was able to reduce oxidative stress in neuronal cells via transcriptional regulation of antioxidant (SOD and catalase) and apoptosis (AKT, nuclear factor kappa beta [NF-Kβ], extracellular signal-regulated kinase [ERK] 1/2, c-Jun N-terminal kinase [JNK], p53 tumor suppressor gene, and p38 mitogen activated protein kinase [MAPK]) genes. Apoptosis is often the end result of oxidative stress, and may underlie oxidative stress complications. Regulation of both processes indicates that germinated brown rice may be useful in diseases where oxidative stress-induced apoptosis is a problem, including neurodegerative and cardiometabolic diseases (Kannan and Jain, 2000; Chandra *et al*., 2000).

Furthermore, the reduced oxidation of LDL by germinated brown rice may greatly contribute towards reduced risk of CVD, as we have demonstrated (Imam *et al*., 2014). Plasma F2-isoprostanes, important markers of oxidative stress with significant clinical implications, were equally suppressed by germinated brown rice. Elevated levels of F2-isoprostanes and oxidised LDL (ox-LDL) are closely related, and reflect the high levels of oxidative stress and increased risk of cardiometabolic diseases, while reduced levels can greatly lower such risks (Berliner and Heinecke, 1996; Moore *et al*., 1995). Overall, oxidative stress promotes damage through reactive free radical species, which can be scavenged by antioxidants. When left unchecked, oxidative stress through excess free radicals may eventually lead to disease conditions and complications (Aruoma, 1998). The strong anti-oxidative effects of germinated brown rice demonstrated by its ability to transcriptionally regulate oxidative stress-related genes, therefore, suggest it could reduce the risk of oxidative stress related chronic diseases including CVD, diabetes and neurodegerative diseases.

Nutrigenomic Effects of Germinated Brown Rice on Menopause Related Problems

There are an increasing number of women that reach menopause due to better living standards and improved healthcare delivery. With increased longevity, there is need to improve quality of life of these women, especially since hormonal imbalances cause not only physical but also emotional and psychological disturbances in addition to increased risk of diseases (Barrett-Connor, 1992). Additionally, other life stresses including bereavement, loneliness, depression and anxiety may complicate the lives of these women. Hormone replacement therapy (HRT) has been used for some of these menopausal problems. However, HRT has not been effective

at managing all menopause-associated problems, and may even increase the risks of CVD, cancers and other diseases (Beral *et al.*, 2002). These issues necessitate search for newer alternatives, and germinated brown rice has shown promise in this regard. In the past, germinated brown rice was reported to improve memory and cognition, possibly because of its rich GABA content (Mamiya *et al*., 2004; Mamiya *et al*., 2007; Zhang *et al*., 2010). GABA is an inhibitory neurotransmitter that may elicit anti-depressant and anti-anxiolytic effects (Kalueff and Nutt, 2007), and may produce similar properties due germinated brown rice, although it is likely that other bioactive compounds play a role in these effects.

Germinated brown rice was able to regulate uterine expression of estrogen related genes (estrogen receptor-beta (ER-β), calcium-binding protein (CaBP9k), complement protein (C3), heat shock protein 70 kDa (HSP70), and interleukin (IL)-4 receptor), suggesting that it may have some estrogen-like activity on the uterus. Moreover, increase in glandular and luminal epithelial cells of the uterine and vaginal wall suggested that germinated brown rice may prevent against vaginal dryness, atrophy and discomfort. Also, osteoporosis is a serious problem in menopause, and germinated brown rice was shown to up-regulate genes involved in bone formation in an osteoporosis animal model. It was able to transcriptionally regulate bone metabolism genes in ovariectomised animal model, including bone morphogenic protein-2 (BMP-2), secreted protein acidic and rich in cysteine (SPARC), runt-related transcription factor 2 (RUNX-2), osteoblast-specific transcription factor osterix (Osx), periostin, osteoblast specific factor (Postn), collagen 1&2 (Col1&2) and calcitonin receptor gene (CGRP) (Muhammad *et al*., 2013; Muhammad *et al*., 2013).

The absence of any documented side effects due to germinated brown rice indicates that it could be used to improve menopausal

problems by women without risking complications like cancers and CVD, as reported for HRT. Also, regulation of cardiometabolic risk by germinated brown rice is beneficial for menopausal women since they are at risk of such diseases due to loss of estrogen (Rosano *et al*., 2007; Carr, 2003). The implications of these observations for menopoausal women are potentially enormous, and may reverse some of the problems associated with menopause due to estrogen deficiency.

Nutrigenomics implications of Germinated Brown Rice on Alzheimer 's Disease

Alzheimer's disease (AD) is a progressive disorder of the central nervous system, with huge economic burden to individuals and societies (Selkoe *et al*., 2012). It has been proposed that antioxidants have huge potentials in preventing and/or delaying the development of neurodegenerative diseases (Di Matteo *et al*., 2007). Additionally, supplementation of germinated brown rice improved learning and memory and confer protection against neurodegenerative changes induced by the neurotoxic Aβ (Mamiya *et al*., 2004; Zhang *et al*., 2010, Mamiya *et al*., 2013). Germinated brown rice was shown to reduce depression and depression-like behaviors mainly through the regulation of BDNF and serotonin levels in brain (Mamiya *et al*., 2007; Zhang *et al*., 2010; Nakajo *et al*., 2011). Accordingly, the extract of germinated brown rice primarily consisting of GABA showed high antioxidant potentials, increased neuronal cells viability, reduced mitochondrial membrane potential, and prevented phosphatidylserine translocation and eventually neuronal apoptosis (Ismail *et al*., 2012; Soi-ampornkul *et al*., 2012; Soi-ampornkul *et al*., 2013). Germinated brown rice also attenuated oxidative effects of H_2O_2, implied by reduced LDH release, intracellular ROS generation, upregulated the expression of antioxidant genes (SOD1,

SOD2 and catalase) as well as reduced oxidative stress biomarkers such as lipid peroxidation and δ-aminolevulinic acid (Zhang *et al*., 2010; Mamiya *et al*., 2013; Azmi *et al*., 2015). Attenuation of cognitive and memory deficits by germinated brown rice is likely due to its regulatory mechanisms on apoptotic, antioxidative and NMDA receptor cascade pathways [Ismail *et al*., 2012; Soi-ampornkul *et al*., 2012; Soi-ampornkul *et al*., 2013; Azmi *et al*., 2013; Mamiya *et al*., 2014]. Moreover, increase in mRNA levels of AKT, NF-KB and ERK, and decrease in those of JNK, p38 and p53 due to germinated brown rice suggested that it had anti-apoptotic and pro-survivals effect on neuronal cells [Azmi *et al*., 2013]. Germinated brown rice also modulates transcription of AD-related genes such as Presenilin 1, BACE1, BACE2, ADAM10, LRP and Neprilysin (Azmi *et al*., 2015), implying that it is able to modulate Aβ processing pathway, increase clearance of Aβ from the brain into bloodstream [Shibata *et al*., 2000] and contribute towards Aβ degradation (Iwata *et al*., 2000). It also alters the structure of Aβ further suggesting anti-amyloidogenic effects (Azmi *et al*., 2015). Since germinated brown rice could target multiple mechanisms (Figure 5), its intake could have profound implications and provide optimism that hopefully leads to the preventive management for AD in future.

In aggregate, germinated brown rice mediate its effects by regulating transcription of genes and their products in various disease processes. The resultant improvement in metabolic indices through multiple mechanisms may be beneficial in many disease processes. Also, synergism of the bioactives in germinated brown rice likely mediates its functional effects, in agreement with the concept of food synergy; the effects of the germinated brown rice as a whole may be contributed by the effects of the individual compounds as well as their arrangement in the germinated brown rice matrix (Imam *et al*., 2012; Sani *et al*., 2012).

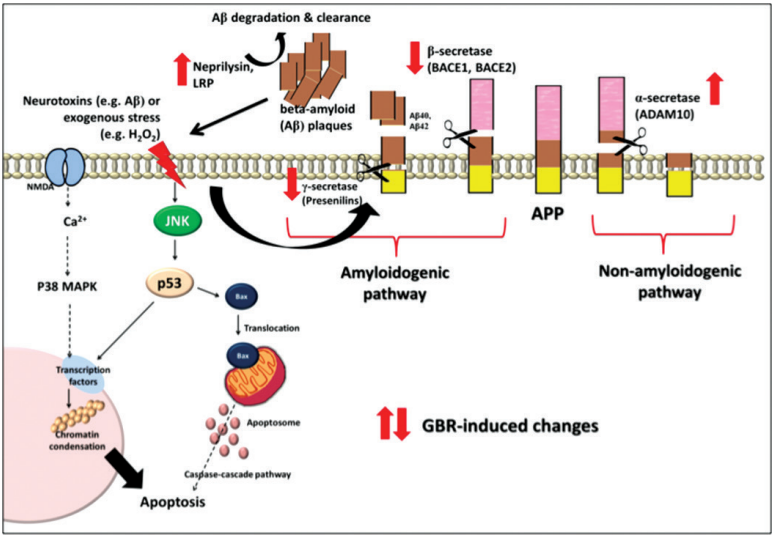

Figure 5 Proposed schematic diagram showing targets of germinated brown rice (GBR) in APP processing metabolism pathway. ADAM10: A Disintegrin and metalloproteinase domain-containing protein 10; APP: amyloid precursor protein; BACE: beta-site APP-cleaving enzyme; Bax: BCL2-associated X protein; H_2O_2: hydrogen peroxide; JNK: c-Jun N-terminal kinases; LRP: Low density lipoprotein receptor-related protein; p53: p53 tumor suppressor.

(*Reference:* Azmi et al., 2015).

Hence, the overall effect of the food may not be explained by the effect of only one of its bioactives. This is in agreement with our findings on the effects of germinated brown rice bioactives on the expression of PPARγ; individual bioactive compounds upregulated the expression of the gene, while in combination they downregulated its expression (Imam *et al.*, 2013). These multiple mechanisms underlying the effects of germinated brown rice may mean better metabolic outcomes when compared with single bioactive compounds or even pharmacological agents. Germinated brown

rice could, therefore, serve as an efficient alternative to white rice, and as an adjuvant for the management of many chronic diseases especially when consumed on a long term to provide continuous supply of bioactives. Consumption of germinated brown rice instead of white rice in rice consuming countries may reduce the overall burden of disease in view of the health benefits of germinated brown rice documented thus far and the risks of cardiometabolic diseases due to white rice consumption. There is need for more long term studies and policy changes in rice consuming countries in order to provide the health benefits of germinated brown rice to as many people. Importantly, very little resistance will be expected from these populations since white rice is already their staple food.

BIOACTIVE-RICH FRACTIONS AS NUTRACEUTICALS: OUR CONTRIBUTIONS

The concept of bioactive- rich fractions is somewhat similar to that of food synergy (Jacobs, 2009; Jacobs and Tapsell, 2007), in which it is claimed that food and not nutrients is the fundamental unit in nutrition. Its proponents claim that through synergy of bioactive compounds in food, better nutritive value is derived than what individual nutrients would provide. In bioactive-rich fraction, it is conceived that the lead bioactive compound in the presence of other metabolites, even in small amounts, will produce more beneficial effects. As various compounds are derived from a single source, a better functional effect is attained.

SUPERCRITICAL FLUID EXTRACTION (SFE) FOR PRODUCTION OF BIOACTIVE RICH FRACTION

The challenge in preparing bioactive rich fractions is applying the right technology for their extraction. Organic solvents are normally used in the chemical, pharmaceutical, food, cosmetic and nutraceutical industries. However there is an increasing public awareness of the health, environment and safety hazards associated with the use of organic solvents in extraction and the possible solvent contamination of the final products. The high cost of organic solvents and the increasingly stringent environmental regulations together with the new requirements of the pharmaceutical and food industries for ultra-pure and high added value standardised extracts, have pushed for the need to use new and clean technologies for the processing of nutraceuticals. Supercritical fluid extraction using carbon dioxide as a solvent has provided an excellent alternative to the use of organic solvents. Over the past decades supercritical CO2 has been used for the extraction and isolation of valuable bioactive compounds from natural products.

SFE is a process in which the extractant is being isolated from the matrix using supercritical fluids and near critical fluids, which is a substance when above its critical temperature, acts as the solvent. The supercritical solvent, now saturated with the extracted product, is expanded to atmospheric conditions and the solubilised product is recovered in the separation vessel permitting the recycle of the supercritical solvent for further use. This type of solvent has added a new dimension to conventional organic solvent due to their density-dependant solvent power which can easily be suited to the process needs by regulating such parameters as temperature, pressure, flow rate and/or composition. Other important properties of supercritical fluids are their low surface tensions, low viscosities and moderately high diffusion coefficients.

We have often used SFE for the preparation of nutraceuticals in our work both as extracts and bioactive rich fractions at laboratory or pilot scales (Figure 6). We found that supercritical CO2 can be selective in the separation of our desired compounds from plant resources without leaving toxic residues and without the risk of thermal degradation of the extracts. Through the exploitation of the solvating power acquired by carbon dioxide near the critical points and the sensitivity of this power to small perturbations in temperature, pressure and modification of the solvent, bioactive rich fractions are readily obtained due principally to the high volatility of carbon dioxide at ambient conditions. The favourable transport properties of CO2 near the critical point also allows deeper penetration into solid plant matrix making the extraction more efficient and faster with higher yield compared with conventional organic solvents. This technology was shown to be specifically ideal for our work in extracting and fractioning oils. Work by Diaz-Maroto *et al.* (2002) has also shown that SFE is especially effective in the separation of high quality essential oils and its derivatives for use in the food, cosmetics, pharmaceutical and other related industries, producing high-quality essential oils with commercially more satisfactory compositions (lower monoterpenes) than obtained with conventional hydro-distillation due to its closed system.

These advantages may make supercritical carbon dioxide extraction more superior and ideal for preparation of bioactive rich fractions especially those that are volatile. SFE has more significant advantages compared to conventional extraction which include:

- Superior end-products:
  * Undegraded extracts
  * High concentration of desired active compounds with no residual solvents

    * Longer shelf-life and free from microbial contaminants

- Superior process:
    * Simultaneous extraction and fractionation of extracts is possible
    * Flexible operating conditions for multiple product extractions
    * Carbon dioxide (CO2) as solvent – Generally Regarded As Safe (GRAS) solvent

For the past two decades, the commercial application of SFE remained restricted to few products due to high investment costs and for being new and unfamiliar operation. With advances in the process, equipment and product design and realization of the potentially profitable opportunities in the production of high added value products, industries are becoming more and more interested in supercritical fluid technology.

Figure 6 Supercritical Fluid Extraction System used in our work for preparation of Bioactive Rich Fractions. The extraction is carried out in high-pressure vessel at selected parameters in which CO_2 is put in contact with the material from which a desirable product is to be separated and fractionated. The supercritical solvent, now saturated with the extract, is expanded to atmospheric conditions and the solubilized extract is recovered in the separation vessel permitting the recycle of the supercritical solvent for further use.

Several studies including our own work have reported the health promoting and disease- preventing effects of single bioactive compounds and compared such effects to those of corresponding rich fractions or rich extracts. Most of the studies, however, are still at preclinical stage. Nevertheless, bioactive-rich fractions had overall better functional effects than single compounds in the management of chronic diseases. Hence, we hypothesise that the isolation and use of bioactive-rich fractions from plant sources instead of single bioactive compounds may be a way of maximising

health benefits from plants bioresources and could be advocated among researchers working in ethno-, phyto-, complementary and alternative medicine fields.

Standardisation of the composition, nevertheless, poses as a big challenge in rich fraction production. The preparation of rich fraction is focussed upon the concentration of the lead compound, while other minor bioactives are not considered as much. Our experience has shown that the minor bioactives either work additively or synergistically with the lead compound, thereby producing better functionality. Non-standardisation of the phytochemicals may result in different rich fractions with varied efficacies, leading to batch by batch product variability. The complexity of plant starting materials used in the production may also affect the process and rich fraction. This is an issue that must be closely considered if rich fractions were to have any clinical significance. A well-validated analytical methodology, comprising of standardised sample preparation and sensitive chromatographic analytical tools, is needed for compositional analysis and fingerprinting purposes. By standardising and monitoring the chemical compositions of the rich fraction, product variations would be minimised and the quality of the product would be enhanced. In this regard, the use of the green extraction technology, SFE could reduce product variations and, in the process minimal hazards, associated with residual solvent used for extraction, to humans and the environment.

Our team has contributed to expanding understanding of the efficacies of nutraceuticals in this regard. However, most studies are still in preclinical stages (Table 4), and we have recently embarked on clinical trials to understand clinical relevance of these nutraceuticals. The use of bioactive-rich fractions instead of single bioactive compounds may be a way to maximise the health benefits obtained from plants bioresources.

Table 4 Summary of studies comparing single bioactive compounds to respective rich fraction

Compound/ rich fraction	Method of preparation of rich fraction	Study design	Summary of findings	Reference
TQ/TQRF	Supercritical fluid extraction, 600 bars, 40°C	Effects of 2 ppm TQ and 80 ppm TQRF (containing 2 ppm TQ) on expression of APO A1 and APO B100 genes in HEPG2 cells were evaluated.	TQRF upregulated APO A 1 gene and downregulated APO B100 gene significantly more than TQ (at lower equivalent concentration)	Al-Naqeeb and Ismail, 2009
TQ/TQRF	Supercritical fluid extraction, 600 bars, 40°C	Hypocholesterolemic effect of TQ (20, 50 and 100 mg/kg body weight) and TQRF (0.5, 1.0 and 1.5 g/kg body weight) in high-fat-diet fed Sprague Dawley rats following 8-week intervention.	Both TQ and TQRF showed equal hypocholesterolemic effect (no significant difference) at a dose-dependent manner. TC and LDL were significantly decreased in TQRF and TQ groups compared to untreated group. Plasma TC and LDL levels of TQRF and TQ treated rats were significantly lower compared to control group	Al-Naqeeb *et al*., 2009

TQ/TQRF	Supercritical fluid extraction, 600 bars, 40° C	Effects of 2 ppm TQ and 80 ppm TQRF (containing 2 ppm TQ) on expression of LDLR and HMGCR genes in HEPG2 cells were evaluated.	TQRF upregulated LDLR gene and downregulated HMGCR gene significantly more than TQ	Al-Naqeeb *et al*., 2009
Vanillin/VRF	Supercritical fluid extraction, 600 bars, 80° C	Antioxidant capacities of vanillin and VRF were evaluated, and their effects (100 ppm of vanillin, and 100 and 200 ppm of VRF) on LDLR and HMGCR genes were determined.	VRF showed better antioxidant activities than vanillin using BCB and DPPH assays. At 100 ppm, VRF upregulated LDLR gene and downregulated HMGCR gene better than vanillin did. Higher concentration (200 ppm) of VRF was more effective at regulating genes.	Al-Naqeeb *et al*., 2010
TQ/TQRF	Supercritical fluid extraction, 600 bars, 40° C	Effects of TQ (20, 50 and 100 mg/kg body weight) and TQRF (0.5, 1.0 and 1.5 g/kg body weight) were evaluated, after 8 weeks of feeding, on antioxidant capacity of hypercholesterolemic rats	Within the range of doses tested, TQRF was better than TQ at reducing LDL, and significantly improving liver hydroxyl radical scavenging activity and upregulating antioxidant genes.	Ismail *et al*., 2010

Gamma-oryzanol/ ORF	Supercritical fluid extraction, 600 bars, 40° C	Regulation of gene expression related to antioxidant and oxidative stress in stressed Sprague Dawley rats by gamma-oryzanol and ORF.	ORF demonstrated greater antioxidant activity than gamma-oryzanol through regulation of antioxidants and oxidative stress related genes.	Ismail *et al.*, 2010
TQ/TQRF	Supercritical fluid extraction, 600 bars, 40° C	Cytotoxicity of TQ and TQRF on colon cancer (HT29), lymphoblastic leukemia (CEMSS) and promyelocytic leukemia (HL60) were evaluated	TQRF was more cytotoxic on all cells (IC50 values for HT29, CEMSS and HL60 cells were 400, 350 and 250 µg/ml) when compared to TQ (IC50 values of 8, 5 and 3 µg/ml, respectively) Less or equal equivalent concentrations of TQ in TQRF showed almost equal rate of apoptotic cells compared to pure TQ	Norsharina *et al.*, 2011

Thymoquinone Rich Fraction

Nigella sativa is known to be rich in several bioactive compounds, including fatty acids, sterols, thymoquinone (TQ), polyphenols, tocopherols, minerals, and vitamins (Venkatachallam *et al*., 2010; Nergiz and Ötleş, 1993), which effectively act against several pathological processes. Among them, TQ is considered to be an active component responsible for many of the antioxidant properties of *N. sativa*. However, other bioactive compounds are also known to potentiate the effects of TQ, as we have demonstrated recently (Al-Naqeeb and Ismail, 2009; Al-Naqeeb *et al*., 2009; Al-Naqeeb *et al*., 2009).

Through *in vitro* experimentation, we have demonstrated the effects of 2 ppm TQ against 80 ppm of a thymoquinone-rich fraction (TQRF containing 2 ppm TQ) on the expression of cholesterol-related genes (APO A1 and APO B100) in HEPG2 cells (Al-Naqeeb and Ismail, 2009). The results indicated that the TQRF is able to favorably regulate cholesterol metabolism through upregulation of the APO A1 gene and downregulation of the APO B100 gene to a significantly greater degree than the same concentration of TQ present in the TQRF when used alone. Similarly, my team have shown that TQRF more effectively upregulates the low-density lipoprotein receptor (LDLR) gene and downregulates the 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) gene compared with TQ (at the same concentration present in the TQRF) (Al-Naqeeb et al., 2009). Using an animal model, however, no significant differences were observed when TQ and a TQRF with the same TQ content were administered to high-fat diet-induced hyperlipidemic rats for 8 weeks (Al-Naqeeb *et al*., 2009). Total cholesterol (TC) and low-density lipoprotein (LDL) were significantly decreased in the TQRF and TQ groups compared with the untreated group. Plasma TC and LDL levels in the TQRF- and

TQ-treated rats were significantly lower compared with the positive control group. Interestingly, another study by my team (Ismail *et al*., 2010) has evaluated the effects of TQ (20, 50 and 100 mg/kg body weight) and a TQRF (0.5, 1.0 and 1.5 g/kg body weight) on antioxidant capacity in hypercholesterolemic rats, reporting that the TQRF shows better efficacy at reducing LDL and significantly improves liver hydroxyl radical scavenging activity. The mechanistic basis for the improvements in the antioxidant statuses of the rats has been demonstrated to involve the upregulation of hepatic antioxidant genes and enzymes, in which TQRF exposure results in higher expression levels compared with TQ.

Furthermore, the cytotoxicities of TQ and the TQRF on colon cancer (HT29), lymphoblastic leukemia (CEMSS) and promyelocytic leukemia (HL60) cell lines were evaluated in a study conducted by my team (Norsharina et al., 2011). The TQRF was reported to possess more potent cytotoxic activity on all cancer cell lines assessed compared with TQ because the TQRF, which contained less TQ, caused an equal proportion of apoptotic cells.

Oryzanol Rich Fraction

Rice bran, which is a by-product of the rice milling process, has been discarded as waste in the past. However, it has been demonstrated to contain high amounts of fat and protein as well as secondary metabolites, including γ-oryzanol (a mixture of ferulic acid esters of triterpene alcohols and sterols), tocols (tocopherols and tocotrienols), unsaturated fatty acids, phytosterols, stanols and policosanols (Ha *et al*., 2005; Irmak and Dunford, 2005; Jariwalla, 2001; Jeng *et al*., 2011; Laokuldilok *et al*., 2011). Rice bran contains up to 300 mg/kg of vitamin E and ~3000 mg/kg of gamma-oryzanol which is a mixture of 10 ferulate esters of triterpene alcohol. Oryzanol has been reported to contribute to multiple health beneficial activities,

including, reduction of cholesterol levels, inhibition of platelet aggregation, and antioxidant functions (Ismail *et al*., 2010). Rice bran may potentially impart anti-oxidative, anti-inflammatory, cholesterol-lowering, anti-diabetic, anti-cancer, anti-hypertensive and other beneficial effects on humans (Laokuldilok *et al*., 2011; Hudson *et al*., 2000; Kaup *et al*., 2013; Shirakawa *et al*., 2007). Reports have shown that most functional properties of rice bran oil are associated with its oryzanol content. Oryzanol rich fraction (ORF) was the first bioactive rich fraction prepared and patented by our team using the SFE technology (Figure 7).

Figure 7 E-Ory - Oryzanol Rich Fraction

We have demonstrated the effects of ORF extracted from rice bran using SFE compared with those of oryzanol on the regulation of hepatic antioxidant and oxidative stress-related genes in distressed Sprague-Dawley rats (Ismail *et al*., 2010). After subjecting the animals to 10 weeks of stressful swimming exercise, the rats were administered the ORF at 125, 250 and 500 mg/kg body weight or oryzanol at 100 mg/kg body weight for a period

of 5 weeks. The results indicated that the ORF possessed greater antioxidant activity than oryzanol, and this effect was mediated through the regulation of antioxidants and oxidative stress-related genes.

Vanillin Rich Fraction

Our team has evaluated the capacities of 100 ppm vanillin and 100 and 200 ppm of a vanillin-rich fraction (VRF) on antioxidant gene expression in addition to the expression of the LDLR and HMGCR genes (Al-Naqeep *et al*., 2010). In this study, the VRF was shown to have better antioxidant activities than vanillin alone. Furthermore, the VRF upregulated LDLR and downregulated HMGCR more effectively than vanillin in a dose-dependent manner. Our work on VRF has also shown its anti-carcinogenic activity in azoxymethane induced colon cancer in rats (Ho *et al.*, 2012).

Phenolic Acid Rich Fractions

Standardisation of herbal extract is intended to ensure batch by batch consistency in the final products. However, there is much debate over the process of herbal extract standardisation due to the abundances of phytochemicals. Nevertheless as mentioned previously, the development of the bioactive-rich fraction represents efforts to maximise the potential of bioactive components while facilitating and easing the process of standardisation (Ismail *et al*., 2010; Imam *et al*., 2015). In line with the government policy and Malaysia being one of the megadiverse countries of the world, we had worked on several local herbal plants for their phenolic rich fractions including *Molineria latifolia, Clinacanthus nutans,* and *Schismatoglottis bauensis* to name a few.

Molineria latifolia (Dryand. ex W.T.Aiton) Herb. ex Kurz, also known locally as *lemba* or *lumbah*, is a perennial herb with tuberous root and categorised under family Hypoxidaceae. The plant is distributed throughout the range from China (Guangdong) to Malaysia, generally found on the slightly shady forest floor of both primary and secondary forests (The Plant List, 2013; Govaerts, 2016). One of the most captivating finding on *M. latifolia* is the unique sweet-tasting and taste-modifying properties of the fruits. The ability to trigger sweet taste from sour materials is due to the presence of curculin. The active form of curculin, termed neoculin, is a heterodimer comprising of two monomers linked by two disulphide bonds. The sweet taste elicits by curculin is approximately 550 times sweeter than sucrose on weight basis. A more intense sweet taste, however, is evoked under acidic condition (Koizumi *et al.*, 2015; Ohkubo *et al.*, 2015). Treatment combining fruits and rhizome extracts in a one to one ratio on experimental rats carried out by our team had previously been demonstrated to improve glucose and lipid metabolisms (Ishak *et al*., 2013). Preliminary studies proposed that the anti-diabetic efficacy may potentially be contributed by curculigoside and cinnamic acid in the rhizome.

Curculigoside and cinnamic acid rich fraction (CCAF) had been prepared from the rhizome of *Molineria latifolia* via a simple bio-guided fractionation process. Interestingly, enriching the phenolic contents of the rich fraction, in particular curculigoside and cinnamic acid, tremendously improved the antioxidant properties and protection against oxidative damages. Treatment of standardised CCAF on experimental diabetic rats had revealed its ability to modulate oxidant-antioxidant balance. Transcriptional studies had demonstrated concerted actions of standardised CCAF on both KEAP1-NRF2 and PKC/NF-κB signalling in the adipose

tissue. On the other hand, both *in vitro* and *in vivo* studies had also indicated the capability of standardised CCAF to attenuate hyperglycaemia. A 32-day intervention on experimental diabetic rats effectively modulated glucose tolerance and improved lipid profiles. Improvement in the glycaemic response and lipid lowering efficacy of standardised CCAF had been associated with modulation of insulin sensitivity. Hepatic translational studies demonstrated increased phosphorylation of AKT at Ser473, coupled with increased tyrosine phosphorylation but decreased serine phosphorylation of IRS1. Additionally, i*n vitro* studies using differentiated 3T3-L1 cells showed that the rich fraction increased the availability of GLUT4 transporter at the plasma membrane of the adipocytes, in part via the activation of AKT and mTOR signalling cascades at the molecular levels. Simultaneous protective effect of standardised CCAF against hyperglycaemia and oxidative stress may pose for extra advantages. More studies, however, are still needed to further substantiate the therapeutic efficacy of standardised CCAF for type 2 diabetes mellitus management.

In addition, our group has also patented the preparation and use of proto-catechuic acid (PCA) rich fractions from *Clicanthus nutans* or commonly known as Sabah snake grass. PCA rich fractions containing 6 folds higher PCA relative to the crude extract showed tremendously improved antioxidant properties to modulate oxidant and antioxidant balance (Sarega *et al*., 2016).

PCA rich fraction treated human monocytes cell (THP1) also showed remarkable higher cholesterol efflux. Additionally, *in-vitro* hepatic transcriptional studies demonstrated significant inhibition of 3-hydroxy-3-methylglutaryl-CoA reductase genes involved in cholesterol synthesis pathway, while remarkably upregulated low density lipoprotein receptor which is involved in clearance of low density lipoprotein and also upregulated the

expression of key gene involved in lipid metabolism, peroxisome proliferator-activated receptor alpha in PCA rich fraction treated human hypercholesterolemia cell model. Based on the regulation of multiple metabolic perturbations, PCA rich fraction from *C. nutans* is potentially a better alternative to currently used statins for the management of hypercholesterolemia, although future clinical trials are needed to ascertain its clinical efficacy.

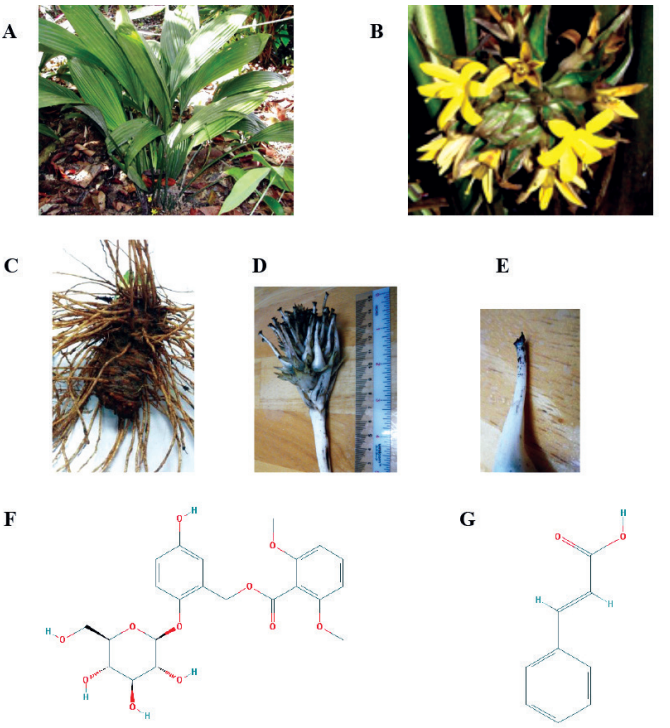

Figure 8 M. latifolia and its major bioactives. (A) M. latifolia plant. (B) M. latifolia flower. (C) M. latifolia rhizome. (D) A bunch of M. latifolia fruits. (E) Single M. latifolia fruit. (F) Curculigoside. (G) Cinnamic acid. (National Center for Biotechnology Information, 2016)

In aggregate, only a limited number of bioactive compounds have been compared with their rich fractions, most of which were carried out by my team (Imam *et al*., 2015). Mechanistic insights into the functional effects of bioactives have been provided in some cases, showing that the rich fractions are more effective than the single bioactive compounds in regulating the expression of genes. Our studies and others have shown that rich fractions are better than single bioactive compounds largely attributable to the synergistic effects of the multiple bioactive compounds in the rich fractions (Imam *et al*., 2015). Moreover, the extraction of rich fractions is potentially more cost-effective compared with the isolation of pure compounds because the former process does not require extensive purification. By standardising and monitoring the chemical compositions of rich fractions, product variations would be minimised, and product quality would be enhanced. In this regard, the use of the green extraction technology SFE could reduce product variations with minimal hazards to humans and the environment, such as those associated with the residual solvents used for extraction. My team has taken tremendous advantage of this technology, to maximally extract bioactive compounds from plants and foods, with minimal harmful effects to the environment and biological systems.

The Future of Medicinal Plants must Focus on Bioactive Rich Fractions

The plants that served as sources of nutraceuticals prior to the recent developments were not intended for such purposes. As such, most of them are not available in commercial quantities sufficient to be cultivated and used for disease prevention, without causing hazards to humans and other life forms. Interest in the study and use

of plant bioresources is largely fuelled by the biodiversity present in any country. In view of the promising findings from the plant bioresources present in Brazil, Bolzani *et al.* (2012) argue that the biodiversity of Brazil offers a great opportunity for the use of plant bioresources for medicinal purposes, while Aremu *et al.* (2012) also argue that the lack of adequate antihelminthic agents and the abundance of promising medicinal plants in South Africa is enough reason to focus attention on the search for a treatment from those plants for the poorer South African populations afflicted by diseases. These opinions may also be valid for many countries enriched with biodiversity including Malaysia. However, we are faced with a dilemma: whether to harness the protective properties of these plants or maintain the balance of the ecosystem by leaving them unperturbed. Plants have roles to play in maintaining a balanced ecosystem. Cultivating them for use as nutraceuticals will mean disturbing the natural balance that exists in an already fragile ecosystem and risking the increased effects of global warming. However, the world cannot afford to allow people to die from chronic diseases when there are natural, God-given and affordable remedies that will effectively reduce morbidity and mortality from such diseases. Therein lies the major problem of fighting chronic diseases while at the same time exposing the Earth to the detrimental effects of adverse climate change. This issue will therefore need to be explored pragmatically to strike a balance that will not endanger the existence of any life form on Earth.

For many years, there has been a global environmental threat largely caused by human activities that produce greenhouse gases. These gases are known to affect the environment adversely and are therefore a hazard not only to humans but also to other life forms. Human industrial activities such as mining, driving cars that produce excessive amounts of gas, and other activities are

the main causes for the destruction of the ozone layer. The ozone layer is thought to protect all life forms on Earth from adverse environmental effects, and its destruction may be highly detrimental for the inhabitants of Earth. In addition, the destruction of the ozone layer exposes humans and other life forms on Earth to adverse environmental conditions, including extremes of temperatures, melting polar ice caps leading to floods and erosion. There are also risks of other adverse effects on the physical environment and plants. Environmental temperature stressors can affect the secondary metabolites and other compounds produced by plants (Kirakosyan *et al*., 2003; Zobayed *et al*., 2005). For instance, *Rhodiola rosea,* which is a medicinal plant used in Europe, Asia, and North America for the treatment of a wide variety of ailments including fatigue, depression and infections, is now believed to be extinct due to climate change (Brown *et al*., 2002; Cavaliere, 2009). Cavaliere also describes in detail how climate change has influenced medicinal and aromatic plants (Cavaliere, 2009). He maintains that climate change has caused a tremendous effect on the life cycles and distribution of the world's vegetation, including wild medicinal and aromatic plants.

The world is already facing problems from climate change and global warming. Deforestation has also increased, and commercial harvesting of available plant sources for their nutraceutical properties will only increase environmental hazards, potentially causing more problems than solutions (Culas, 2009). However, as more studies unravel the potential of plants in the management of chronic diseases, the natural temptation will be to harvest and harness every available source within reach. This will tilt the balance in the ecosystem toward higher amounts of atmospheric carbon dioxide and lower oxygen due to reduced plant populations. The continued massive use of medicinal plants and a concurrent lack

of or disregard for legislation to control it may soon lead us to a realisation that we had taken for granted the importance of plants in maintaining a balanced ecosystem. The temptation to harvest plants proven to have medicinal value may create a void that will push global warming and its effects further. It is my conviction that nanotechnology and bioactive rich fractions can provide some answers to the problem of over-cultivation of plant bioresources. Studies from my team and those of other researchers have shown that nanonisation and the use of bioactive rich fractions can enhance bioactivity of a compound thus reducing the need to use higher doses in managing a disease. Moreover, the side effects profile of nanoparticles and rich fractions show low toxicity compared with standard compounds due to lower concentrations of the compounds in the extracts.

ON-GOING JOURNEY FROM R&D TO COMMERCIALISATION

Commercialisation is the process that converts ideas, research, or prototypes into viable marketable products that retain the desired functionality. These products are usually designed to be readily manufactured at low cost and launched quickly with high quality. Commercialisation also involves formulating the manufacturing and supply chain strategies, devising implementation plans, and implementing such plans. It may be a necessary step for commercial success for innovations coming from startup ventures or company research efforts. It comprises several stages and usually takes a considerable amount of time, conscious efforts and money. This process also consists of the technical, commercial, and financial steps that are necessary for the successful development and marketing of new or improved products and the commercial use of new or improved processes. Thus commercialisation in my opinion

can be highly challenging as it requires a whole convoluted series of journeys involving technological and scientific path, from basic research through to a final warranted product, and all the various proof points along the way: principle, concept, viability, scalability, value and quality.

The "How-to" of Technology Acquisition, Innovation and Entrepreneurship initiative is a new learning curve for majority of Malaysian researchers including our team. Thinking commercial does not come naturally to us previously. Majority of researchers do not see the applications of their R&D in the commercial world or recognise the problems that industry is trying to solve. However as researchers we are under increased pressure from the government and the public to commercialise our research findings for income generation through royalty streams, licensing fees or taxation revenue generated by new industrial enterprises. Some researchers have succeeded in responding to this new expectation, while others are still experiencing and yet many have met with obstacles. To make it worse, there exists the concept of a valley of death that prevents the progress of science from the laboratory bench to the point where it provides the basis of a commercially successful business or product. The valley of death describes the point where a business, often a technology based business, has a working prototype for a product or service that has not yet been developed enough to earn money through commercial sales. The company needs to find sufficient money to develop the prototype until it can generate sufficient cash, through sales to customers that would allow it to be self-sufficient and grow.

Following the successful demonstration of the functional effects of germinated brown rice and some bioactive rich fractions, we took the challenge and came up with some products for the market. These include OryGold™ (germinated brown rice-based products)

and HSGold™ (TQRF-based products), which have been on the market only recently and soon TQGold Nano™ . These products have received numerous medals at organisational, national and international levels. Naturally, patents followed these successes, and the desire to bring the benefits of my rich fractions and functional foods lead to the creation of start-up companies in conjunction with UPM: Orygold Sdn Bhd and Nutracreme Sdn. Bhd, where I am both Technical Director for the companies.

HSGold™

Malaysian government under various ministries especially Ministry of Science, Innovation and Technology (MOSTI) and Ministry of Education (MOE) has supported and provided some funds to carry out not only R&D activites but also bridging funds to enhance commercialisation. As the project leader, we managed initially to secure MTDC-Special CRDF to develop antioxidant rich fraction from rice bran (E-Ory) using Supercritical Extraction Technology which we purchased using this grant. The same technology is currently used to manufacture Thymoquinone Rich Fraction, a novel nutraceutical, extracted from Nigella sativa seeds (HSGold™) for Nutracreme Sdn. Bhd. This patented closed system technology is able to trap and concentrate 10 times more Thymoquinone plus other bioactives which conventional methods are not able to perform. The advantages of SFE as mentioned earlier are that the extraction process is non-toxic and the end product is not contaminated. HSGold™ is highly efficacious and thus has the capacity to maintain optimum health with anti-aging properties. It is scientifically proven to have high antioxidant activity, cardioprotective, anti-diabetic properties and aids in the prevention of Alzheimer's disease. HSGold™ can be used as an excellent ingredient in across the industries including pharmaceutical, cosmetic, food and health.

It can be formulated for food, beverage and cosmetic products as preservative, antioxidant and flavouring or as a health supplement.

Thymoquinone rich fraction can also be packaged as nanoemulsion for improved bioavailabilty, efficacy and applications (TQGold Nano™). The reason for the creation of this new product is to overcome delivery problem so that thymoquinone delivery and uptake to target tissues especially the brain can be increased for slowing down the progress of Alzheimer's disease (AD). Thus, nanodelivery system may provide a possible solution to overcome these challenges by affording targeted bioactives delivery, enhancing bioavailability, improved solubility and efficacy of TQRF as well as prolonged its pharmacological effects in comparison to conventional formulations. Since TQGold Nano™ is formulated with emulsifier, which are approved for human consumption (generally regarded as safe), they can be taken orally. TQGold Nano™ is prepared by homogenizing lipid phase containing the active substance TQRF and aqueous phase containing a surfactant, such as Tween 80, and passing the mixture through a high-pressure homogeniser.

Both HSGold™ and TQGold Nano™ have practical application in a multitude of commercial areas, such as the chemical, pharmaceutical and cosmetic industries. The current innovations can be used in the management of type 2 diabetes, which currently affects 346 million people globally and more than 1.4 million Malaysians (1 in 5 adults in Malaysia). Also, it may have potential application in management of chronic diseases in which oxidative stress and hypercholesterolemia are implicated. It can be easily used in the cosmetics for anti-aging and functional food formulations as preservative and anti-oxidant.

This technology won various prestigious awards nationally and a gold medal at an International Exhibition, between 2009 and 2012, while the work has been published in more than 30 ISI

journals, many of which are in Q1 journals. TQGold ™ has also been market validated by Frost & Sullivan as well as Biotechcorp. Commercialisation of HSGold[tm] was part of Symbiosis programme, an initiative from Ministry of Education and Universiti Putra Malaysia with funding from Malaysian Technology Development Corporation (MTDC).

Figure 9 HSGold, TQGold Nano and TQRF

OryGold™

Malaysia's current population is growing steadily at an annual rate of about 1.95%. The country has seen a steady increase in the standard of living and with it, its purchasing power (per capita income exceeds RM19,739 or US$5681). Lifestyle changes have led to an increase in the demand for convenience foods and healthy

foods. Increasing consumer awareness in nutrition value and food fortification for healthcare has created the demand for functional/ healthy minimally processed fresh food, organic food and natural food flavours from plants and seafood. Certainly a growing demand for premium food items can be predicted, indicated by the increasing living standards and purchasing power of the modern Malaysian population.

The overall process of germination of brown rice in this innovation therefore, provides a cost-efffective way of improving the benefits of rice. However, because not all people consume rice, and because of the growing consumer interest in functional beverages, producing germinated brown rice drink is seen as a way to bring the benefits in germinated brown rice to the wider consumer market. This has the potential to provide instant energy for all ages and also provide enhancement in health and prevention from diseases. Already, there are projections by leading monitors in the functional food industry that functional beverages have the most prospects among all the emerging functional foods.

The world's population is facing increasing health and resource constraints. Particularly, combination of ageing populations, changing lifestyles and surging rates of chronic diseases is putting undue pressure on economies around the world. And as the cost of treating chronic illness and age-related conditions such as Alzheimer's disease continues to rise, greater emphasis is being placed on the importance of prevention rather than cure. In this regard, the need for solutions (increasingly food and drink based) that help consumers maintain good health into old age has increased. Simultaneously, changing lifestyles and diets are contributing to a rapid growth in obesity and other chronic lifestyle diseases, giving a further boost for the need for healthier diets. According to the World Health Organisation, by 2020, chronic diseases will account

for almost three-quarters of all deaths worldwide. Increasingly, individuals will be expected to take more responsibility for managing their own health. There are, however, already clear signs that consumers welcome solutions that give them more control. Moreover, as family structures and lifestyles change, many of the positive food values that were centred on family meal times in the home have also slowly changed. Parents themselves are under increasing time, energy and financial pressures making it more of a challenge to provide nutritious and affordable family mealtimes. Making sure good diet starts from childhood and re-building positive "relationships" with food will be a key part of safeguarding the health of future generations. Despite being under increasing pressure, parents will continue to be focused on securing the best possible start in life for their children. Food and drink will play a key part in this, particularly as we develop a greater understanding of the importance of nutrition throughout a child‟s development. For the future, foods with simple-to-understand ingredients, nutritious, tasty, and those that are natural and provide the needed energy and health benefits across all ages will receive more patronage.

With these prospects in mind, we have developed and commercialised OryGold™ as an instant healthy beverage with GBR as the main ingredient. It is formulated to provide satiety and impart health benefits at the same time. Euromonitor International reports that the functional beverages' market is increasing from the estimated growth of 18% between 2011 and 2016. There are already several of these products and more continue to be commercialised. However germinated brown rice based drink is still new. Because of its properties, its prospects are considerably bright.

OryGold™ is designed to appeal to those groups of people who are considering its health benefits especially among the older generation. Its effects on metabolic control and antioxidant status

would provide the fragile systems of the older generation with the much needed support and protection. Other age groups can also benefit from it, further increasing its potentials. The product versatility may also incorporate several fruits and vegetables especially for children in order to provide the recommended daily servings with ease. It is believed that the natural source of these fruits partly increases the appeal of OryGold™. With proper product positioning and strong marketing strategy, OryGold™ prospects are considerably bright and hopeful.

Figure 10 ORYGOLD from Germinated brown rice

Commercialisation is not an easy journey though can be interesting. There are many challenges and hurdles need to be tackled. For a business to be successful it must, over time, generate more money than it spends. However, the timescale for achieving a positive cash position can be lengthy. Technology companies like Nutracreme Sdn. Bhd. and OryGold Sdn. Bhd. often need to invest heavily in terms of time, energy and money before they can demonstrate the

potential to be profitable. If they cannot find patient investors, then they may go out of business or be forced to sell out cheaply before they realise their potential.

CONCLUDING REMARKS

With the rising incidence of chronic diseases and the need for natural and potent treatment alternatives, plant bioresources have become major sources of bioactive extracts. To maximise natural benefits, bioactive-rich fractions have been developed that contain not only a major bioactive compound but also other bioactives that synergistically contribute to their functionality. There appears to be evidence that synergism due to multiple bioactive compounds is responsible for the enhanced functional effects of rich fractions compared with single bioactive compounds. Furthermore, germinated brown rice is a health food developed as a consequence of trying to improve the hard texture of brown rice, as a healthier substitute for white rice. Its enhanced bioactive composition has been shown to produce better functional effects than brown rice and white rice, including antihyperglycemic, hypocholesterolemic and antioxidant. Nutrigenomic studies have provided insights into how these properties are mediated by germinated brown rice bioactives likely through food synergy. In the areas of functional foods (germinated brown rice) and nutraceuticals (bioactive rich fractions), my team has contributed in revolutionising perceptions about the use of these products for health promotion and disease prevention. My attempts at commercialisation, though challenging, will hope to ensure that benefits from these products will be brought to the general public.

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BIOGRAPHY

Maznah Ismail, who was born in Tapah, Perak in 1956 is the eldest of five siblings. She started schooling at Sek. Kebangsaan Teruntum in Kuantan, followed by secondary education in a full residential school at Sek. Tun Fatimah, Johore Bahru, where she had completed Malaysian Certificate of Education. She was offered a scholarship by Majlis Amanah Rakyat (MARA) to pursue her studies for A-levels in Southend-on-sea, England. She graduated with B.Sc (Hons) in Biochemistry from University of Salford, England, M.Sc in Biochemistry with minor in Nutrition from Louisiana State University, Baton Rouge, U.S.A and Ph.D in Nutritional Biochemistry from Faculty of Medicine, University of Glasgow, Scotland. She has served UPM for more than 35 years and currently is a Professor of Nutritional Biochemistry at the Faculty of Medicine and Health Sciences as well as the Head of Laboratory of Molecular Biomedicine, Institute of Bioscience. Prior to this appointment she had served as department head (1994-2002) at the same Faculty and Director of Interim Institute of pharmaceuticals and nutraceuticals, MOSTI (2004-2006).

She received a Commonwealth fellowship as a visiting Professor at the Health Sciences Faculty, University of Manitoba, Canada, and the International Atomic Energy Agency (IAEA) fellowship as a visiting scientist at the Institute of Food Research, Norwich, UK in 2002. Later she obtained other IAEA fellowships for scientific visits between 2007 – 2009 to University of Dublin, and Trinity College, Ireland and later to Free University Berlin, Germany where she had developed research collaboration on nanotechnology and nanodelivery with Prof Muller and Prof Keck who own many of patents in nanotechnology.

Maznah has received more than 60 awards at organisational, national and international levels. At national level she received

Anugerah Tokoh Pekerja Perempuan Negara (2006) and Public Service Innovation Award by the Prime Minister's Department, Malaysian Toray Science Foundation (MTSF) Award, Excellent Researcher Award by Ministry of Education and Bioinnovation Award by MOSTI. Maznah has also received four times Vice Chancellor Fellowship Awards from UPM for three different categories (Excellence in Research in 2005 & 2012), Best Paper Award in 2013 and Innovation and Commercialisation (2014) categories. In addition, she received *Anugerah Penyelidik Cemerlang* from the Faculty of Medicine & Health Sciences and Institute of Bioscience. Three of her research products were recognised internationally when she was awarded with 2 gold medals and one bronze at IeNa International Exhibition, Nuremberg, Germany and at the 32nd *International Exhibition of Inventions, Techniques and Products* in Geneva, Switzerland.

Throughout her teaching career at UPM, Maznah had helped in curriculum development, restructuring of academic units, human resource development, teaching medical modules and health science courses for the undergraduates and supervising graduate students. There is no doubt however; her special interest has always been on research and innovation, focusing on Nutraceutical development, Nutrigenomics and Nanodelivery. Much of her research work has been centred on development of novel nutraceuticals in the form of bioactive rich fractions from natural resources including agricultural recycled materials such as rice bran and kenaf seeds. Bioactive rich fractions were also prepared from herbs local or imported. Her interest in the use of the green technology, supercritical fluid extraction, has warranted the extraction and fractionation of bioactive rich fractions as nutraceuticals for their efficacy and economic value. She draws a lot of her inspiration from the "waste to health and wealth" concept which forms the basis for her strong desire

to contribute to improving the well-being of humanity and at the same time conserve the already endangered and ailing ecosystem, as reflected in the scope of her work. These efforts have led her to carve a niche for herself in the fight against chronic diseases, using natural resources, in recognition of the significant contribution of these diseases to the overall global burden of diseases. Her desire to impact on the lives of vast majority of people around the world who succumb to chronic diseases is a major force that keeps her going, and her major achievements reflect this. She has to her credit works on antidiabetic, cardioprotective, anticancer and cognitive-enhancing properties of functional foods and nutraceuticals. Her work on germinated brown rice is particularly worthy of note. She cherishes this technologically simple, cost-effective yet health promoting functional food that promises a lot for the global rice eating population which makes up over half the population of the world and hopes that when it gains wide acceptance among the vast majority of this population, the benefits would be enormous.

Her passion for research and innovation has awarded her and her team with research grants from the government including MOE, MOSTI and EPU with pre-commercialisation funds from MTDC and from private companies like Bernas Sdn. Bhd. Mediherbs Sdn Bhd and more recently from Biotropics Sd. Bhd and Perusahaan Azan Sdn Bhd. As a project and programme leader she has received about RM 20 million in grants to support 35 intensive research in novel nutraceutical development at preclinical and clinical trial stages, 2 bridging funds and 2 commercialisation grants. Much of her effort is now being concentrated on commercialising some of these prototypes including Germinated Brown Rice (OryGold^{TM}) and Thymoquinone rich Fraction (HSGold^{TM}), while rice bran antioxidants (E-ORY) , formulated rice bran oil (RiBO) and kenaf bio oil are kept in view. Commercialisation of HSGold^{TM} is made

possible through Graduate Enterpreneur Symbiosis programme between UPM-MOE and funded by MTDC, while market validation was done by Biotechcorp-Frost & Sullivan. Maznah has so far filed or been granted 15 patens on her work.

With her research team, Maznah has published 8 chapters in books, over 250 papers in refereed journals, majority in Q1 and Q2 journals, and more than 150 citations in proceedings. One of her articles "Nutrigenomic effects of germinated brown rice and its bioactives on hepatic gluconeogenic genes in type 2 diabetic rats and HepG2 cells" published in Jurnal *Molecular Nutrition and Food Research*, 2013, 57 (3):401-411, Q1, received Best Article Category for Vice Chancellor Fellowship Award in 2013. This article has described for the first time the mechanism of anti-diabetic and genetic regulatory activity of bioactive rich fractions of germinated brown rice. Maznah works closely in research with her collegues, especially research officers, postdocs and junior lecturers whom she mentors as well as graduate students. As the main supervisor, Maznah has in total 43 students (27 PhD, 16 MSc), 30 of them have graduated. About half of her students are from abroad. Laboratory of Molecular Biomedicine where she is the Head, has been a ground for research training for local and international scientists, students and staff alike. Likewise, some of her PhD students have received fellowships for research placement at international labs while others have received awards at international conferences for their presentations.

It has always been Maznah's hope and aspiration to be able to serve UPM and the country to her best ability in line with UPM's slogan "With Knowledge We Serve" through research, teaching, creation and dissemination of new knowledge and marketable product. She is married with 4 children and 5 grandchildren.

ACKNOWLEDGEMENTS

" In the Name of Allah the Beneficent , the Merciful"

The ultimate gratitude, devotion and dedication surely belongs to Allah SWT.

This manuscript represents part of a milestone in more than two decades of my research work at UPM, specifically in the Faculty of Medicine & Health Sciences, National Interim Institute of Pharmaceutical & Nutraceutical, Ministry of Science, Technology and Innovation, Malaysia and presently at the Laboratory of Molecular Biomedicine, Institute of Bioscience. Throughout these years, research has basically shaped out my life since half of my age has been spent in the Lab being surrounded by various people who share the same kind of love and passion for research. To these wonderful people I would like to acknowledge their vast contribution and their amazing spirit for teamwork, diligence, sharing and kindness.

First and foremost I would like to extend my gratitude to the top management of UPM specifically the past and present Vice Chancellor , Ybhg Prof Datin Paduka Dr Aini Ideris and Deputy Vice Chancellor of Research & Innovation, Ybhg Prof Dato' Abu Bakar Salleh and Ybhg Prof Dato' Mohd Azmi Mohd Lila, and his teams for having sound policy and guidelines for research, development and innovation. The previous and the present Deans of Faculty of Medicine & Health Sciences, Ybhg Prof. Dr Norlijah Othman and Ybhg Prof Dato' Abdul Jalil Nordin as well as Ybhg Prof Dr Fatimah Mohd Yusof and Ybhg Prof Dr Abdul Rahman Omar being Directors of IBS are fully acknowledged for their strong support and encouragement.

Dozens of people have helped in contributing at various levels of research work including co-researchers, research officers,

research associates, research fellows, research assistants and most of all my postgraduate students and postdocs. I would like to extend my deepest gratitude to Ybhg Prof Fatimah Mohd Yusof, Ybhg Prof Dr Mahiran Basri, Ybhg Prof Dr. Rozi Mahmud, Ybhg Prof Dr Hamidon Basri, Ybhg Prof Dr Abd Rahman Omar, Ybhg Prof. Dr Conny Keck, Ybhg Prof Abdel Basit Mariod, Ybhg Prof Dato Nik Muhammad Nik Abd Majid, Assoc Prof Dr Faridah Qamaruzzaman, Assoc Prof Dr. Norhaizan Md Esa, Dr Maizatun Atmadini Abdullah, Dr Norhasnida Zawawi, Dr Norakmal, Mr. Chan Kim Wei, Dr Nor Asmah Abd Razak and Norsharina Ismail.

Special appreciation goes to my postdoc and postgraduate students who have spent hours and hours in the lab day and night. These are Dr. Mustapha Umar Imam , Dr Ragu and Dr Shahid , while among postgraduate students include Dr Zaki A.H Tubesha, Dr Ismaila Mohd Sani , Dr Nur Akmal Ishak, Dr Siti Aisyah Abdul Ghaffar, Dr. Ho Ket Li, Dr Zhang Yida, Dr Hoe Zhiping, Assoc Prof. Dr Loh Su Peng, Assoc Prof Dr Azrina Azlan, Dr Fatimeh Abedini, Dr Aminu Isahaka, Dr Nicholas Kong Mun Hoe, Dr Ghanya Naji Muhammad Al-Naqib, Oii Der Jiun, Rachael Serega Nadarajan, Nurfarhana, Nurhanisah Mohd Azmi, Lian Chee, Wong Wai Teng, Waffa Wallad, Nik Nurhasanah, Hafeez, Abubaka, Ramlah, Nurnadia, Norzila Motidayen, Sima Alishavende, Adamu Hadiza Altine, Mariamu Nyako Kura, Bil Yaminu Abu Bakar and Hafeez Muhammad Yakasai.

Besides R&D, commercialisation activities have now occupied part of my time. Since it is a new venture for academics, it can be time consuming, difficult and challenging. I extend my gratitude to PSP and Innohub teams especially Assoc Prof Dr Samsilah, Dr Wan Norhayati, Dr Zaki and En Zakir and enterprenurs, Mohd Khidir Tan Sri Musa and Salahuddin.

My acknowledgements further go to the sponsors of my R&D work which include MOSTI, MOE, UPM, and private companies such as Bernas Sdn Bhd, Azan Foods Sdn Bhd., Koperasi Bernas Sdn Bhd., Biotropics Sdn Bhd, Beckman Coulter (USA) and ABSciex (Singapore). Our commercialisation activities through the setting up of 2 start-up companies, namely Nutracreme Sdn Bhd and OryGold Sdn Bhd are being funded by MTDC via Symbiosis Program. I greatly appreciate MTDC's commitment to our start-up.

I am indebted to my staff at The Laboratory of Molecular Biomedicine for their understanding, help and comradeship for which I am forever thankful. They are Mastura, Norhayati, Zainura, Siti Muskinah, Abidin and Mohd Hanif.

To my family, especially my husband, Dr Abu Bakar Hamidon and my children and daughters/son in-laws; Muhammad Firdaus Abu Bakar & Noor Puspamarina Radzali, Muhammad Faruq Abu Bakar & Siti Fazreena Dato Shamsuhar, Dr Faizah Abu Bakar & Mohd Khidir Tan Sri Musa, Muhammad Faris Abu Bakar & Farrah Alina Abd Rais, thank you for your love, support and prayers.

" With Hardship Comes Ease, Indeed With Hardship Comes Ease"

In the Shade of Al-Quran by Sayyid Qutb, Surah 94, Ash Sharh (Solace), Ayat 5 & 6

"Kalau tidak Dipecahkan Ruyung, Manakan Dapat Sagunya"
Peribahasa Melayu

May Allah bless us all.

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   The Challenge to Communication Research in Extension
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   Indigenous Materials and Technology for Low Cost Housing
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   11 December 1993

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   Engineering Technological Developments Propelling Agriculture into the 21st Century
   28 May 1994

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    Rock, Mineral and Soil
    18 June 1994

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    6 August 1994

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    Oil Pollution in the Malaysian Seas
    24 September 1994

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    Fine Chemicals from Biological Resources: The Wealth from Nature
    21 January 1995

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    25 February 1995

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25 March 1995

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6 May 1995

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Bahasa Melayu sebagai Bahasa Ilmu-Cabaran dan Harapan
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14 October 1995

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28 October 1995

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9 December 1995

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2 March 1996

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29 June 1996

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27 July 1996

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16 November 1996

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Plant Biotechnology - Strategies for Commercialization
21 December 1996

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10 July 1999

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14 August 1999

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23 October 1999

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24 June 2000

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27 April 2002

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27 June 2002

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Blueprint for Transformation or Business as Usual? A Structurational Perspective of the Knowledge-Based Economy in Malaysia
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13 September 2003

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Respiratory Tract Infection: Establishment and Control
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Cocoa-Wonders for Chocolate Lovers
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High Temperature Superconductivity: Puzzle & Promises
13 March 2004

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Oils and Fats Analysis - Recent Advances and Future Prospects
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24 April 2004

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Tapping the Power of Enzymes-Greening the Food Industry
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28 August 2004

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27 May 2005

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Smart Partnership: Plant-Rhizobacteria Associations
17 June 2005

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From the Soil to the Table
1 July 2005

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Materials Science and Technology: Past, Present and the Future
8 July 2005

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Enhancing Career Development Counselling and the Beauty of Career Games
12 August 2005

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26 August 2005

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23 December 2005

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27 January 2006

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Haemorrhagic Septicaemia in Cattle and Buffaloes: Are We Ready for Freedom?
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3 March 2006

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Internet Unwired
24 March 2006

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Development and Innovation in the Fracture Management of Animals
31 March 2006

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Strategic Feeding for a Sustainable Ruminant Farming
19 May 2006

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Green Organic Chemistry: Enzyme at Work
14 July 2006

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Towards Large Scale Unconstrained Optimization
20 April 2007

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22 June 2007

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Econometric Modelling for Agricultural Policy Analysis and Forecasting: Between Theory and Reality
13 July 2007

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Managing Change - The Fads and The Realities: A Look at Process Reengineering, Knowledge Management and Blue Ocean Strategy
9 November 2007

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Expert Systems for Environmental Impacts and Ecotourism Assessments
23 November 2007

102. Prof. Dr. Saleha Abdul Aziz
Pathogens and Residues; How Safe is Our Meat?
30 November 2007

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Hubungan Sesama Manusia
7 December 2007

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Planning for Equal Income Distribution in Malaysia: A General Equilibrium Approach
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1 August 2008

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Penjagaan Kesihatan Primer di Malaysia: Cabaran Prospek dan Implikasi dalam Latihan dan Penyelidikan Perubatan serta Sains Kesihatan di Universiti Putra Malaysia
8 August 2008

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Memanfaatkan Teknologi Maklumat & Komunikasi ICT untuk Semua
15 August 2008

118. Prof. Dr. Md. Salleh Hj. Hassan
Role of Media in Development: Strategies, Issues & Challenges
22 August 2008

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Gender in Everyday Life
10 October 2008

120 Prof. Dr. Mohd Shahwahid Haji Othman
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