DEVELOPMENT OF NUTRACEUTICAL TABLET FROM RED DRAGON FRUIT *Hylocereus polyrhizus* (Weber) Britton & Rose

By

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Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Master of Science

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Chairman : Associate Professor Siti Salwa Abd Gani, PhD
Faculty : Agriculture

Nutraceuticals are products derived from food sources with added health benefits. They have gained much interest among the public, who take the products to improve and maintain optimal physical and mental conditions. The present study was conducted to characterize nutritional content of *Hylocereus polyrhizus*, locally known as *Buah Naga Merah,* and subsequently develop a nutraceutical product that is dietary supplement in the form of tablets with potential medicinal or health benefits. This fruit has become increasingly popular worldwide due to its vitamin and mineral compositions as well as antioxidative properties. Dietary supplement in the form of tablets is accepted and trusted by manufactures and consumers alike thus an ideal way for nutrients and antioxidants to be administered and consume. Water extraction was conducted on fruit pulp and tested on its nutritional composition, chemical constituents, antioxidant properties, mineral and heavy metal contents and cytotoxicity. Nutritional composition was measured using proximate analyses which consists of ash, crude protein, crude fiber, moisture content and pH, while, chemical constituents were determined using Gas Chromatography-Mass Spectrometry (GC-MS). Antioxidant properties were tested using eight different antioxidant in-vitro models namely Total Phenolic Content (TPC), Total Flavonoid Content (TFC), Betacyanin Content (BC), 2,2-diphenyl-1-picrylhydrazyl (DPPH) Radical Scavenging Activity, 2,2'-azino-bis (3-ethylbenzothiazoline-6 sulfonic acid) (ABTS) Radical Scavenging Activity, Ferric Reducing Antioxidant Power (FRAP), β-Carotene Bleaching (β-CB) and Phosphomolybdate Assays (PA). Inductively Coupled Plasma-Mass Spectrometry (ICP-MS) were used to evaluated the metal and heavy metal contents while cytotoxicity activity was examined using Brine Shrimp Lethality Bioassay (BSLB). In the formulation of *H. polyrhizus* tablets, five variables were studied namely magnesium stearate (0.2 – 1% w/w), menthol (0.2 – 1% w/w), lemon powder (1 – 10% w/w), maltodextrin (5 – 10% w/w) and glucose (37.5 – 53.1% w/w). The effects of components variables on the hardness of tablets were analyzed using a D-

Optimal Mixture Experimental Design (D-Optimal MED) statistical software. Results of proximate analyses showed that water extract of the pulp had 0.67±0.02 g/100g ash, 1.39±0.01 g/100g crude protein, 1.82±0.06 g/100g crude fiber, 87.52±0.07 g/100g moisture and pH value of 4.7. No fat constituent was detected. Chemical constituents of pulp showed that the volatile pattern was due to by-products of sugar degradation and Maillard reactions. TPC, TFC and BC were recorded at 32.90±0.92 mg GAE/100mL, 2.26±0.14 mg QE/100mL and 18.21±2.51 mg/100mL of extract, respectively. Free radical scavenging activity, that is DPPH and ABTS protocols, were 73.38±2.24% and 92.66±0.22%, respectively. FRAP, β-CB and PA recorded values of 132.17±3.74 µmol Fe^{2+}/100ml, 74.41±4.84% and 28.94±0.83 mg AAE/100mL of extract, respectively. Metal and heavy metals data of the pulp were compared with the maximum admissible limit in drinking water by World Health Organization (WHO) and all elements investigated were below the acceptable limit suggesting that the fruit is non-toxic. The pulp also displayed no cytotoxicity activity, indicating that the fruit is safe for consumption. In the tablet formulation, D-Optimal MED gave predicted hardness of tablet at 8.5 kg/cm^2. The optimal inputs were established as follows: magnesium stearate (0.66% w/w), menthol (0.74% w/w), lemon powder (6.15% w/w), maltodextrin (7.61% w/w) and glucose (44.34% w/w), with the actual hardness of the optimized tablet recorded at 8.581 kg/cm^2. The study demonstrated the potentiality of *H. polyrhizus* as a dietary supplement with therapeutic properties for general consumers well-being.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Master Sains

PEMBANGUNAN TABLET NUTRASEUTIKAL DARIPADA BUAH NAGA MERAH *Hylocereus polyrhizus* (Weber) Britton & Rose

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Nutraseutikal adalah produk diperbuat dari sumber makanan yang ditambah dengan faedah kesihatan. Produk nutraseutikal mendapat banyak permintaan dalam kalangan masyarakat terutama kepada yang mengambil produk untuk memperbaiki dan mengekalkan kesihatan fizikal dan mental yang optimum. Kajian ini telah dijalankan untuk mencirikan kandungan nutrisi dalam *Hylocereus polyrhizus*, yang dikenali dengan nama tempatan *Buah Naga Merah*, dan seterusnya membangunkan makanan tambahan dalam bentuk tablet yang mempunyai potensi perubatan atau faedah kesihatan. Buah ini menjadi semakin popular di seluruh dunia kerana kandungan vitamin dan mineral serta sifat antioksidannya. Makanan tambahan dalam bentuk tablet diterima dan dipercayai oleh pengeluar dan pengguna, oleh itu menjadi cara yang ideal untuk nutrien dan antioksidan diberikan dan dimakan. Pengekstrakan menggunakan air telah dijalankan ke atas isi buah dan diuji untuk kandungan nutrien, unsur kimia, sifat antioksidan, kandungan mineral dan logam berat serta kesitotoksikan. Kandungan nutrient buah diukur dengan menggunakan analisis proksimat yang terdiri daripada abu, protein kasar, serat kasar, kandungan kelembapan dan pH manakala unsur kimia ditentukan dengan menggunakan gas kromatografi-jisim spektrometri (GC-MS). Sifat antioksidan buah diukur menggunakan lapan model *in-vitro* antioksidan yang berbeza iaitu jumlah kandungan fenolik (TPC), jumlah kandungan flavonoid (TFC), kandungan betasianin (BC), aktiviti pembersihan radikal bebas *2,2-diphenyl-1-picrylhydrazyl* (DPPH), aktiviti pembersihan radikal bebas *2,2'-azino-bis (3-ethylbenzothiazoline-6 sulfonic acid)* (ABTS), ujian ferrik yang mengurangkan daya antioksidan (FRAP), pemutihan beta-karoten (β-CB) dan esei fosfomolibdat (PA). Induktif plasma-jisim spektrometri (ICP-MS) digunakan untuk mengukur kandungan logam surih dan logam berat sementara aktiviti kesitotoksikan dinilai dengan menggunakan bioesei kematian udang air masin (BSLB). Dalam formulasi tablet *H. polyrhizus*, lima komponen dikaji iaitu magnesium stearat (0.2 – 1% b/b), mentol (0.2 – 1% b/b), serbuk lemon (1 –

10% b/b), maltodextrin (5 – 10% b/b) dan glukosa (37.5 – 53.1% b/b). Kesan perbezaan jumlah komponen terhadap kekerasan tablet dianalisis menggunakan perisian statistik *D-Optimal Mixture Experimental Design (*D-Optimal MED*).* Hasil analisis proksimat menunjukkan bahawa ekstrak air isi buah mempunyai 0.67±0.02 g/100g abu, 1.39±0.01 g/100g protein kasar, 1.82± 0.06 g/100g serat kasar, 87.52±0.07 g/100g kelembapan dan nilai pH 4.7. Tidak ada unsur lemak yang dikesan. Kajian ke atas profil ekstrak air isi buah dengan menggunakan GC-MS menunjukkan bahawa bahan kimia dalam buah terdiri daripada bahan sampingan hasil dari proses penurunan gula dan reaksi Millard. TPC, TFC dan BC masing-masing dicatatkan pada 32.90±0.92 mg GAE/100mL, 2.26±0.14 mg QE/100mL dan 18.21±2.51 mg/100mL ekstrak. Aktiviti pembersihan radikal bebas, iaitu protokol DPPH dan ABTS, masing-masing adalah 73.38±2.24% dan 92.66±0.22%. FRAP, β-CB dan PA mencatatkan nilai 132.17±3.74 μmol Fe^{2+}/100ml, 74.41±4.84% dan 28.94±0.83 mg AAE/100mL per ekstrak. Data logam surih dan logam berat dibandingkan dengan had maksimum yang dibenarkan dalam air minuman oleh Pertubuhan Kesihatan Sedunia (WHO) dan semua elemen yang disiasat berada di bawah had yang boleh diterima dan menunjukkan bahawa buah itu tidak beracun. Isi buah juga tidak menunjukkan aktiviti kesitotoksikan dan selamat untuk dimakan. Dalam formulasi tablet, D-Optimal MED memberikan ramalan kekerasan tablet pada 8.5 kg/cm^2. Input optimum adalah seperti berikut: magnesium stearat (0.66% b/b), mentol (0.74% b/b), serbuk lemon (6.15% b/b), maltodextrin (7.61% b/b) dan glukosa (44.34% b/b), dengan kekerasan optimum tablet sebenar pada 8.581 kg/cm^2. Kajian menunjukkan potensi *H. polyrhizus* sebagai makanan tambahan bersifat terapeutik untuk kesihatan pengguna am.

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This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Master of Science. The members of Supervisory Committee were as follows:

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LIST OF ABBREVIATIONS

AAE	Ascorbic Acid Equivalent
ABTS	2,2'-Azinobis-(3-Ethylbenzothiazoline-6-Sulfonic Acid
ADI	Acceptable Daily Intakes
AFTA	ASEAN Free Trade Area
ANOVA	Analysis of Variance
API	Active Pharmaceutical Ingredients
ASEAN	Association of Southeast Asian Nation
BBB	Blood Brain Barrier
BC	Betacyanin Content
BCB	β-Carotene Bleaching
BDE	Bond Dissociation Energy
BHA	Butylhydroxyanisole
BHT	Butylhydroxytoluene
BLSB	Brine Shrimp Lethality Bioassay
CAGR	Compound Annual Growth Rate
CAM	Crassulacean Acid Metabolism
COVID-19	Coronavirus Disease 2019
cyclo-DOPA	cyclo-L-(3,4-dihydroxyphenylalanine)
DDMP	2,3-Dihydro-3,5-Dihydroxy-6-Methyl-4h-Pyran-4-One
DF	Dilution Factor
DGRC	Dry Granulation by Roller Compacting
DGS	Dry Granulation by Slugging
DHA	Dihydroxyacetone

DOE	Design of Experiments
DMDP	2,3-Dihydro-3,5-dihydroxy-6-methyl-4h-pyran-4-one
DNA	Deoxyribonucleic Acid
DPPH	2,2-Di (4-Tert-Octylphenyl)-1-Picrylhydrazyl
EPP	Entry Points Projects
ETP	Economic Transformation Program
FBG	Fluid-Bed Granulation
FIM	Foundation for Innovation in Medicine
FOSHU	Foods for Specified Health Use
FRAP	Ferric Reducing Antioxidant Potential
GAE	Gallic Acid Equivalent
GAP	Good Agricultural Practices
GC-MS	Gas Chromatography-Mass Spectrometry
GDP	Gross Domestic Product
GMP	Good Manufacturing Practices
HAT	Hydrogen Atom Transfer
HMF	5-Hydroxymethylfurfural
ICP-MS	Inductively Coupled Plasma-Mass Spectrometry
ISO	International Standard of Organization
LDL	Low-Density Lipoprotein
MED	Mixture Experimental Design
NDD	Noncommunicable Disease
NKEA	New Key Economic Areas
NPRA	National Pharmaceutical Regulatory Agency

PG	Propyl Gallate
QE	Quercetin Equivalent
R^2	Coefficient of Determination
RNS	Reactive Nitrogen Species
ROS	Reactive Oxygen Species
RSE	Relative Standard Error
SET	Single Electron Transfer
SOP	Standard Operating Procedure
TAC	Total Antioxidant Capacity
TEAC	Trolox Equivalent Antioxidant Capacity
TFC	Total Flavonoid Content
TPC	Total Phenolic Content
TBHQ	Tert–Butylhydroquinone
TPTZ	2,3,5-TriPhenyl-1,3,4-Triaza-2-Azoniacyclopenta-1,4-Diene Chloride
UV-Vis	Ultra Violet Visible
WHO	World Health Organization

CHAPTER 1

INTRODUCTION

1.1 Background of Study

In Malaysia, the movement of people from rural settings to urban environments, often termed as urbanization, has indeed presented many benefits in terms of economic, political, cultural and social aspects. Industrial revolution has created countless job opportunities in various sectors such as education, public health, transport, business, food and others. In recent years, the situation has reduced much of the unemployment rate in the country and ensured stable income for households which indirectly greatly improved the standard of livings (Sitharam *et al.*, 2016). Commercial transactions of goods and services, both local and foreign, have ensured steady economic growth which has significantly contributed to the sustainability of incomes and prosperity of the nation (Turok *et al.*, 2013).

However, busy lifestyles in urban settings have remarkably encouraged people to eat fast food which are generally low in nutrients, contain high amounts of sugars, salt and calories. These eating habits have eventually given rise to a number of chronic diseases and other health issues such as obesity, heart disease, high blood pressure and diabetes (Prasanna *et al.*, 2012). The Star (The Star, 22 June 2020) cited that with 15.6 percent of adults being obese, Malaysia stands as the most obese country in Southeast Asia. In a recent survey by National Health and Morbidity Survey (2019), data showed that more than half of adults in the country (50.1 %) were overweight or obese while 29.8 % of children (5-17 years of age) had extra weight, with 14.8 % classified as being obese, making the country's obesity rate alarmingly high. In more recent time, less physical activities due to movement control order imposed by the Government due to Covid-19 pandemic, have not made the situation any better.

Rising costs of medical treatments in the country and elsewhere, coupled with increase in life expectancy have caused extensive campaigns and advertisements by government and manufactures on the beneficial benefits of nutraceutical as complementary medicine. Much have increased public awareness in improving and maintaining overall health and general well-being (Daliri *et al.*, 2015; Tur *et al.*, 2016; Valavanidis, 2016). Since the dawn of time, accumulated literature on experiences and studies on use of plant-based nutraceuticals and nutritional supplements have reported the potential use of medicinal plants in combating numerous diseases and health issues including the more recent pandemic caused by Covid-19 (Ang *et al.*, 2020; Grant *et al.*, 2020; Islam *et al.*, 2020; Mrityunjaya *et al.*, 2020; Zhang *et al.*, 2020a; Zhang *et al.*, 2020b). It has been widely known that the potentials are largely due to rich pool of bioactive compounds contained within the plants systems that help boost

and support general human well-being (Khodadadi, 2015; Brindha, 2016). Knowledge on the potentials of medicinal plants has also elevated people's desire to protect themselves against disease infections, coronavirus disease included.

The plant-based active ingredients in nutraceutical products which come in many forms such as tablets are known to be clinically safe, attractive to the consumers, and have been reported to be less likely to produce unpleasant side effects (Boccia *et al.*, 2020; Santana *et al.*, 2019). Comprehensive clinical studies on chemical compounds isolated from plants to develop nutraceutical products have been continuously reported in the literature. Among the more frequently mentioned is *Hylocereus polyrhizus* or locally known as *Buah Naga Merah. H. polyrhizus are* considered as exotic superfoods as they are rich in antioxidants (Nurmahani *et al.*, 2012; Abd Manan *et al.*, 2019), vitamins and dietary fiber (Nurmahani *et al.*, 2012; Joshi *et al.*, 2020) as well as exhibiting antimicrobial (Tenore *et al.*, 2012; Yong *et al.*, 2017), antidiabetic (Omidizadeh *et al.*, 2014; Abd Hadi *et al.*, 2016), anticancer (Wu *et al.*, 2006; Guimarães *et al.*, 2017) and antiviral (Chang *et al.*, 2020) properties. Interestingly, antioxidants level of *H. polyrhizus* also higher compared to other *Hylocereus* varieties (Chemah *et al.,* 2010; Suh *et al.,* 2014). The seeds of *H*. *polyrhizus* have also been reported to contain phenolic acid metabolites such as sinapic and E-p-Coumatic acids, which have been claimed to possess anti-inflammatory activities (Cha *et al.*, 2013; Zulkifli *et al.*, 2020). Chemical compounds, 1-hexadecene and N-hexadecanoic acid methyl ester with excellent antioxidant properties also have been detected in the peels of the fruits (Vijayakumar *et al.*, 2018). In addition, *H. polyrhizus* (red flesh cultivar) was found to be better accepted compared to *H. undatus* (white flesh cultivar) by farmers basically due its high consumer preferences (Kek Hoe *et al.,* 2020). In addition, antioxidant properties of the flesh of *H. polyrhizus* are found to be higher compared to *H. undatus* (Nurliyana *et al.,* 2010). Considering its popularity and vast therapeutic attributes, fruits of *H. polyrhizus* have high potential to be used as nutraceuticals (functional food) (Joshi *et al.*, 2020).

Nutraceutical is a combination of the word *nutrition* and *pharmaceutical* coined by Dr. Stephen DeFelice in 1989 (Tur *et al.*, 2016; Santana *et al.*, 2019). *Nutraceutical* is an umbrella term for any bioactive food products that are formulated such that they are suitable for treatments or control of diseases or health issues, as well as for maintaining normal physiological functions of consumers. It has been cited that the nutraceutical market in ASEAN (Association of Southeast Asian Nations) countries is one of the fastest-growing markets, especially after the establishment of ASEAN Free Trade Area (AFTA), a trade bloc agreement by ASEAN countries which facilitates economic integration (Tripathi *et al.*, 2020). The field of nutraceutical has also provided a platform for innovators and manufacturers to be creative in fabricating nutraceutical products while meeting the demand from consumers. Tablet is one of the most popular forms of nutraceutical products as it is easy to handle, longer

shelf-life and provides more accurate content dosage because of its compacted nature (Mohamad Zen *et al.*, 2015).

In the present study, extracts of *H*. *polyrhizus* were tested for antioxidant activities and their medicinal capacity by using established antioxidant assays. Nutrients and chemical compositions of the extracts were identified using proximate analysis and Gas Chromatography-Mass Spectrometry (GC-MS). Analyses on heavy metals and toxicity of the extract were conducted by Inductively Coupled Plasma-Mass Spectrometry (ICP-MS) and Brine Shrimp Lethality Bioassay (BSLB) respectively. In tablet formulation, D-Optimal mixture design was used to evaluate the optimal concentrations of the excipient in terms of hardness.

1.2 Problem Statement

Hectic lifestyle of urban population has, to a large extent, forced people to consume fast food which generally lacks of good nutrition. Insufficient time in food preparation or consuming balance diet (food from different food groups such as vegetables, legumes, fruits, grains, protein foods, meat, and dairy) has limited the intake of essential nutrients required for healthy well-being which eventually leads to diseases. The present study was targeted at the use of natural ingredients with bioactive compounds in a formulated tablet form that was safe, effective and convenient for nutraceutical applications. Natural ingredients have been cited to offer both macro- and micronutrients crucial for healthy well-being (Gopalakrishnan, 2019) while tablets are the most acceptable form for consumers compare to other oral dosage forms due to easy to handle and carried around, stable in terms of chemical and physical as well as had accurate consistent content dosages (Mohamad Zen *et al.*, 2015). In addition, the tablets would have the natural colour of the fruit (purple), hence produce an aesthetically elegant yet effective nutraceutical product. This would positively influence consumer perceptions and compliance on taking nutritional supplement in tablet form (Srivastava *et al.,* 2010). The study formulated a tablet form of nutraceutical product loaded with water extract of *H. polyrhizus* fruit pulp. The study hypothesized that the extracts are a good source of active ingredients that can be incorporated in a tablet form following well-reported antioxidant activity and nutrient contents of the fruit (Rebecca *et al.*, 2010; Choo *et al.*, 2011; Nurul *et al.*, 2014; Abd Manan *et al.*, 2019). The challenge of the study was to develop a suitable formulation ensuring efficient oral delivery of active ingredients for nutraceutical applications without compromising the valuable compounds within the fruit. The establishment of an optimized protocol for preparing a successful *H*. *polyrhizus* tablet contributes to the body of knowledge in the preparation of plant-based nutraceutical tablet.

1.3 Objectives

The present study on optimisation of tablets loaded with *H*. *polyrhizus* extract listed the following four objectives:

i. To investigate nutritional and chemical composition of the fruit pulp;
ii. To analyze antioxidant properties of water extract of the pulp using *in-vitro* method;
iii. To evaluate the cytotoxicity and heavy metals of the water extract of the pulp;
iv. To develop *H*. *polyrhizus* tablet as functional food using D-Optimal Mixture Design.

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