

# **UNIVERSITI PUTRA MALAYSIA**

NUTRACEUTICAL ANALYSIS AND FORMULATION OF EDIBLE TABLET CONTAINING Phaleria macrocarpa (SCHEFF.) BOERL FRUIT

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NAJAT NABILAH BT NOOR EZZUDDIN

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

July 2021

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# DEDICATION

I dedicate this thesis purely to my beloved parents, Noor Ezzuddin Ghazali Azmi and Faridah bt Che Mahmood. Not forgotten my siblings and my supervisor. Although during my study I had to overcome my health condition, due to their support mentally and physically, I capable to finished my study on time.



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Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Master of Science

#### NUTRACEUTICAL ANALYSIS AND FORMULATION OF EDIBLE TABLET CONTAINING Phaleria macrocarpa (SCHEFF.) BOERL FRUIT

By

## NAJAT NABILAH NOOR EZZUDDIN

**July 2021** 

#### Chairman : Associate Professor Siti Salwa Abd. Gani, PhD Institute : Halal Products Research

Phaleria macrocarpa is a recent emerging medicinal plant species with numerous nutraceutical prospects. The present study was undertaken to evaluate nutraceutical potentiality and formulate the species-based tablet as part of dietary supplements with a view of providing medical or health benefits, including the prevention and treatment of diseases. The primary aim of the study was to determine its antioxidant activities and their physicochemical properties, followed by optimization of formulation of tablets from fruit extract of *P. macrocarpa*. At the initiation of the study, proximate analyses showed that the extract consisted of 9.4% protein, 21.6% fibre, 5.6% oil, 88.4% moisture content, 10.9% dry matter and 6.3% ash content. The extract recorded antioxidant content of 80.1% free radical scavenging activity (1,1Diphenyl-1-picrylhydrazyl, DPPH) with 92.9% inhibitory concentration  $IC_{50}$  at concentration of 62.5ppm. Ferric reducing antioxidant power (FRAP), total phenolic content (TPC) and total flavonoid content (TFC) recorded values of 5199.02 Fe<sup>2+</sup>/100 mL, 369.1 mg GAE/g, and 89.89 mg QE/100 mL respectively. In the meantime, total anthocyanin, total carotenoid and total phosphomolybdenum yielded 0.49926 mg/L, 0.29 g BET/100g, and 0.05 mg GAE/mL respectively. The study observed that beta-carotene degradation rate increased with decrease in concentration of extract. Cytotoxicity test carried out using MCF-7 cells, MDA-MB-231 cells and A549 cells, showed that methanolic extract gave positive results towards all cells with IC<sub>50</sub> of 280  $\mu$ g/mL and 25  $\mu$ g/mL (hexane extract) for MCF-7 cells, 210 µg/mL for MDA-MB-231 cells, and 70 µg/mL for A549 cells. Brine shrimp lethality dose recorded 10% mortality rate at highest extract concentration of 1000 ppm. However, antidiabetic and antimicrobial activity of the extract did not produce any positive results. In tablet formulation, the effects of maltodextrin, guar gum, and microcrystalline cellulose (MCC) were observed on tablet hardness and fracturability using statistical D-optimal mixture design software and tested using Texture Analyser. The best performance in hardness and fracturability of the tablet was a mixture of 5.028% maltodextrin, 0.472% guar gum, and 34% MCC giving a desirability value of 0.936. The present study evaluated fruit extract of *P. macrocarpa* and successfully



optimized the formulation of the species-based tablet presenting novel solutions to health-related issues.



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

#### ANALISIS NUTRASEUTIKAL DAN FORMULASI TABLET KEMAM YANG MENGANDUNGI BUAH Phaleria macrocarpa (SCHEFF.) BOERL

Oleh

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Julai 2021

#### Pengerusi : Profesor Madya Siti Salwa Abd. Gani, PhD Institut : Penyelidikan Produk Halal

Phaleria macrocarpa adalah satu spesies tumbuhan ubatan yang mempunyai berbagai prospek nutraseutikal. Kajian ini dijalankan untuk menilai potensi nutraseutikal dan merumus tablet berasaskan spesies berkenaan sebagai satu makanan tambahan dengan tujuan mendapatkan faedah kesihatan termasuk pencegahan dan rawatan penyakit. Tujuan utama kajian adalah untuk penentuan tahap aktiviti antioksidan dan sifat fizikokimia, dituruti mengoptimomkan rumusan tablet berasaskan ekstrak buah P. macrocarpa. Pada permulaan kajian, analisis proksimat menunjukkan ekstrak mengandungi 9.4% protin, 21.6% serat, 5.6% minyak, 88.4% kandungan lembapan, 10.9% bahan kering dan 6.3% kandungan abu. Ekstrak mengandungi antioksidan 80.1% free radical scavenging activity (1,1 Diphenyl-1-picrylhydrazyl, DPPH) dengan 92.9% kepekatan perencatan IC<sub>50</sub> pada kepekatan 62.5 ppm. Ferrik mengurangkan daya antioksidan (FRAP), jumlah kandungan fenolik (TPC) dan jumlah kandungan flavonoid (TFC) masing-masing mencatatkan nilai 5199.02 Fe<sup>2+</sup>/100 mL, 369.1 mg GAE/g, and 89.89 mg QE/100 mL. Sementara itu, jumlah antosianin, jumlah karitenoid dan jumlah fosfomolibdenum masing-masing menghasilkan 0.49926 mg/L, 0.29 g BET/100g, and 0.05 mg GAE/mL. Kajian mendapati kadar penurunan beta karotena meningkat dengan pengurangan kepekatan ekstrak. Ujian sitotoksisiti ke atas sel-sel MCF-7, MDA-MB-231 dan A549 mendapati ekstrak metanol memberi kesan positif terhadap kesemua sel dengan IC<sub>50</sub> pada 280 µg/mL dan 25 µg/mL (ekstrak heksana) bagi sel MCF-7, 210  $\mu$ g/mL bagi sel MDA-MB-231, and 70  $\mu$ g/mL bagi sel A549. Dos kematian udang garam merekodkan 10% kadar kematian pada kepekatan ekstrak tertinngi, 1000 ppm. Walau bagaimanapon, aktiviti antidiabetic dan antimicrobial ekstrak tidak menghasilkan keputusan yang positif. Bagi formulasi tablet, kesan maltodekstrin, gam guar dan selulosa mikrokristal (MCC) telah dikaji ke atas kekerasan dan keboleh patahan tablet dengan perisian statistik dalam rekabentuk campuran D-optimum dengan menggunakan Texture Analyser. Keputusan terbaik dari segi kekerasan dan keboleh patahan tablet adalah pada campuran 5.028% maltodekstrin, 0.472% gam guar, and 34% MCC dengan memberi nilai kebolehinginan 0.936. Kajian telah menilai ekstrak buah P. macrocarpa

dan berjaya mengoptimumkan rumusan tablet yang berasaskan spesies, sekaligus mengemukakan satu penemuan novel berkaitan dengan isu kesihatan.



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All praises do to Allah, Lord of the universe. Only by His grace and mercy this thesis can be completed.

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

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# **Declaration by Members of Supervisory Committee**

This is to confirm that:

- the research conducted and the writing of this thesis was under our supervision;
- supervision responsibilities as stated in the Universiti Putra Malaysia (Graduate Studies) Rules 2003 (Revision 2012-2013) are adhered to.

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| AlCl <sub>3</sub>                   | Aluminium Chloride  |
|-------------------------------------|---|
| ANN                                 | Artificial Neural Network                                     |
| ANOVA                               | Analysis of Variance  |
| A549                                | Human Lung Cancer   |
| BCB                                 | Beta-carotene Bleaching                                       |
| BHT                                 | Butylated hydrotoluene  |
| C.V                                 | Coefficient variation   |
| DMSO                                | Dimethyl sulfoxide  |
| DPPH                                | 1,1 Diphenyl-1-picrylhydrazyl                                 |
| FeCl <sub>3</sub> .H <sub>2</sub> O | Iron Chloride   |
| Fe <sub>2</sub> SO <sub>4</sub>     | Iron Sulphate   |
| FRAP                                | Ferric Reducing Antioxidant Power                             |
| FTIR-ATR                            | Fourier Transform Infrared Spectroscopy                       |
| HCI                                 | Hydrochlric Acid  |
| H <sub>2</sub> SO <sub>4</sub>      | Sulphuric Acid  |
| HNO <sub>3</sub>                    | Nitric Acid   |
| IC <sub>50</sub>                    | Lethal Dose   |
| ICP-MS                              | Inductively Coupled Plasma-Mass Spectrometry                  |
| KCl                                 | Potassium Chloride  |
| MCF-7                               | Human breast adenocarcinoma cell, oestrogen receptor positive |
| MCC                                 | Microcrystalline cellulose                                    |
| MDA-MB-231                          | Human breast adenocarcinoma cell, oestrogen receptor negative |
| MS                                  | Mean square   |

| NaOH  | Sodium Hydroxide                  |
|---|-----------------------------------|
| Na <sub>3</sub> PO <sub>4</sub>                     | Sodium Phosphate                  |
| NaOAC   | Sodium Acetate Trigydrate         |
| NaHCO <sub>3</sub>                                  | Sodium Carbonate                  |
| NaH <sub>2</sub> PO <sub>4</sub>                    | Monosodium Phosphate              |
| NaClO   | Sodium Hypochlorite               |
| ((NH <sub>4</sub> ) <sup>2</sup> MoO <sub>4</sub> ) | Ammonium Molybdate                |
| PRESS   | Predicted Residual Sum of Squares |
| SDS   | Sodium Dodecyl Sulphate           |
| SD  | Standard Deviation                |
| SFE   | Supercritical Fluid Extraction    |
| SS  | Sum of Squares                    |
| SSE   | Error Sum of Squares              |
| SST   | Total Sum of Squares              |
| SSR   | Regressiom Sum of Squares         |
| SWE   | Subcritical Water Extraction      |
| RSM   | Response Surface Methodology      |
| TFC   | Total Flavanoid Content           |
| TPC   | Total Phenolic Content            |
| TPTZ  | 2,4,6-Tris(2-pyridyl)-s-triazine  |

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#### **CHAPTER 1**

## INTRODUCTION

#### 1.1 Background of Study

Malaysia is made up from 13 states, of which 11 are located in the Peninsular and two, the States of Sabah and Sarawak are on the island of Borneo. With the generally uniform tropical conditions throughout the year, Malaysia favours growth of many herbaceous medicinal plants that have been, since the dawn of time, used as traditional or alternative medicines for treatments of various health issues. The World Health Organization (WHO) has defined traditional medicines as the amalgamation of knowledge, skills and practices using plants for upkeep the health as well as prevention, diagnosis, enhancement or treatments related to physical and mental illness or issues (Siti *et al.*, 2009; Ci-fen, 1981).

*Phaleria macrocarpa* (Scheff.) Boerl, locally known as *Mahkota Dewa*, is commonly found and grown in Malaysia. *P.macrocarpa* has been described to have the potential in the control of cancer, haemorrhoids, heart diseases, acne, stroke and various skin diseases (Parhizkar *et al.*, 2013). Literature has it that the fruits of the species contain compound called flavonoid, known to give many health benefits. Due to the species nutritional values, many businesses in the production of supplementary dietary products such as coffee as well as tea-based have been developed.

There are many dietary supplements currently available in the market, in the forms of tablets, capsules, liquids, powders, and gels. Dietary supplements are classified as diverse from drugs and they are non-potent. The US Food and Drug Administration (FDA) defined a dietary supplement as an alternative food, generally containing essential nutrients-like vitamins, minerals and proteins (Hooffmann and Manning, 2014). In the pharmaceutical industry, the tablet form, defined as solid unit dosage form of medicament, is one of the most acceptable forms preferred by consumers in comparison to other oral dosage forms. The tablet oral form has been cited to be easier to handle in terms of chemically, physical stability, and portable (Wen and Park, 2011; Gad, 2008).

With that being said, in recent times, *halal* products in the market have been recognized throughout the world and most restaurants put much effort to obtaining *Halal* certificates following knowledge and greater understanding of the terms of *Halal* and *Haram* as prescribed in Islam, the second largest religion in the world. The South-east Asian countries such as Malaysia, Thailand, Singapore, Brunei, Philippines, and Indonesia have fully recognized *halal* products, while China, Japan and Korea have followed suit with many restaurants having *Halal* certificates. China has been the world's recognized supplier in raw traditional herbs and food supplements followed by Indonesia.

According to Malaysia's Halal Standards, food supplements fall under MS 2200:2008 Halal Cosmetic and Personal Care Act, which explicitly spelled out that cosmetics and personal care products are any substances or preparations intended to be topically applied in contact with various external parts of the human body (epidermis, hair system, nails, lips and external genital organs) or with teeth and mucous membranes of the oral cavity. These *Halal* products are permitted to be used under Shariah law on conditions that they fulfil the following obligations (Department of Standards Malaysia., 2008):

- a) Do not comprise or contain any human parts or ingredients derived from there;
- b) Do not comprise of or contain any parts or substances derived from animals forbidden, including accessories derived from animals forbidden to Muslims by Shariah law, to use or to consume *halal* animals which are not slaughtered according to Shariah law;
- c) Do not contain any materials or genetically modified organisms (GMO) which are decreed as *najis* according to Shariah law;
- d) Are not prepared, processed, manufactured or stored using any equipment contaminated with things that are najs according to Shariah law;
- e) During preparation, processing, manufactured or manufacturing, the product is not in contact and physically segregated from any materials that do not meet the requirements stated in items a), b), c) or d); and
- f) Do not harm the consumer or the user.

## 1.2 Problem Statement

In the production of many pharmaceutical products, one ingredient that generally gives doubt to consumers is the gelatin used in the making of products in the form of capsules. A number of studies cited that about 30% of 100 health products in the form of capsules used gelatines from bovine (Abdul et al., 2014). The reports were appalling because halal issues did not take into consideration on food supplements as well as other pharmaceutical products. In the production of products in the form of tablets, one ingredient of importance in tablet coating is stearate which could be from animal sources. In avoiding syubhah thoughts, vegetable-derived coating could be used instead. The concept of *halal* has, in recent years, been attracting global attention because of its recognition as well as a benchmark for safety, hygiene and quality assurance (Ambali & Bakar, 2013). In the past, pharmaceuticals and nutraceutical products were not part of Halal issues. The scenario changed dramatically when consumers became aware on the genuine concept of Halal in all aspects of life. The context of halal in the present study is not only on the ingredients in tableting, but also referring that the produced products are safe, hygienic and not hazardous to human health. In short, the products produced are free from *najis* (dirt or impurity) or contamination, and harmful germs.

At present, nutraceuticals are being produced and widely used all over the world with ingredients such as mangosteen's skin, Tongkat Ali, Kacip Fatimah, misai kucing and others. *P. macrocarpa* is emerging as a recent medicinal plant used to treat several

diseases and health issues due to its being rich in phytochemicals and medicinal properties in the fruits as reported by Altaf et al., (2013). Zhang et al., (2006) cited that *P. macrocarpa* possess mahkoside A, dodecanoic acid, palmitic acid, flavonoid, lignans and sucrose. In recent time, people are more aware of the long-term side effects of synthetic medicines prescribed by hospitals and pharmacies. Hence, nutraceuticals can be as supplementary medicines apart from synthetic medicines and have the potential to be established by Kementerian Kesihatan Malaysia.

The present study contributes to a new nutraceutical product with higher anti-oxidant properties of *P. macrocarpa* as the main active ingredient cited to be rich in antioxidant compounds, good physico- and bio-chemical values and free from any toxic compounds. The study presents an initiative to boost up local agro-industry as and to increase production of nutraceutical tablets with lower and reasonable price. The study has the potential to popularize usage of *P. macrocarpa* as not many are aware of the superior properties of the species as a nutraceutical product.

## 1.3 Objectives of Study

The study was conducted to achieve the following objectives:

- i. To investigate physico-chemical properties of fruit extract *P.macrocarpa* by using Inductively Coupled Plasma-Mass Spectroscopy (ICP-MS), and Fourier Transform Infrared Spectroscopy (FTIR-ATR)
- ii. To determine functional properties of *P.macrocarpa's* fruits;
- iii. To determine antioxidants activities of P. macrocarpa fruit's extract;
- iv. To optimize the formulation of *P. macrocarpa*-based tablet by Mixture Design using Design Expert Software ;

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