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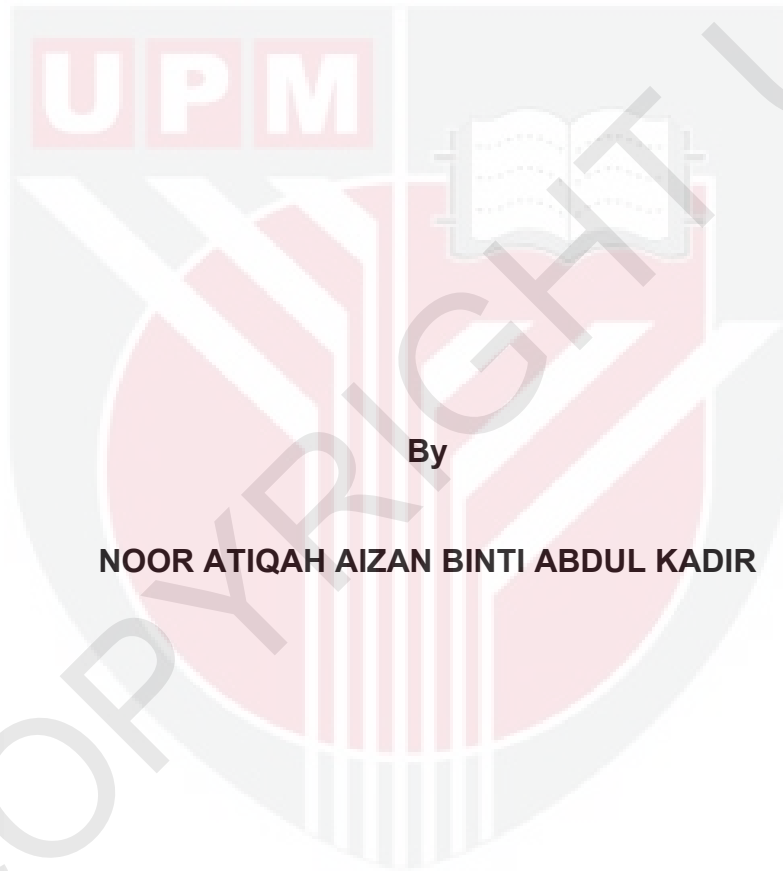
***EFFICACY OF SUPERCRITICAL CARBON DIOXIDE EXTRACTED
DABAI PULP OIL AND DEFATTED DABAI PULP IN
HYPERCHOLESTEROLEMIC SPRAGUE-DAWLEY RATS FOR
CARDIOVASCULAR HEALTH***

NOOR ATIQA AIZAN BINTI ABDUL KADIR

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By

NOOR ATIQAH AIZAN BINTI ABDUL KADIR

**Thesis Submitted to the School of Graduate Studies,
Universiti Putra Malaysia, in Fulfilment of the Requirements for the
Degree of Doctor of Philosophy**

May 2021

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Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfillment of the requirement for the degree of Doctor of Philosophy

EFFICACY OF SUPERCRITICAL CARBON DIOXIDE EXTRACTED DABAI PULP OIL AND DEFATTED DABAI PULP IN HYPERCHOLESTEROLEMIC SPRAGUE-DAWLEY RATS FOR CARDIOVASCULAR HEALTH

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May 2021

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Faculty : Medicine and Health Sciences

Hypercholesterolemia is the hallmark of early cardiovascular diseases (CVDs), and CVDs are the primary cause of death globally. CVDs are attributed the causes of death for an estimated 17.9 million people each year (WHO, 2017). *Canarium odontophyllum* Miq. fruit (dabai) is a novel source for new healthy oil and nutraceuticals. The quality parameters of the supercritical carbon dioxide (SC-CO₂) extracted dabai pulp oil (DPO) such as moisture and volatile content (MVC), free fatty acid content (FFA), iodine value (IV), peroxide value (PV), and fatty acids composition (FAC) were determined. This is the first study to examine the MVC, FFA, IV, and PV in SC-CO₂ extracted DPO. The MVC of DPO was $<0.001 \pm 0.00\%$. Next, the FFA in DPO was $2.57 \pm 0.03\%$, and the IV of DPO was 53.74 ± 0.08 g iodine/100 g oil. Meanwhile, the PV of DPO was 4.97 ± 0.00 mEq/kg. The main FAC of DPO was palmitic acid (41.56 ± 0.10 %), followed by oleic acid (39.37 ± 1.01 %) and linoleic (cis) acid (12.54 ± 1.03 %). DPO was characterised as SFA-rich oil due to its high SFA composition (47.65 ± 0.11 %). DPO also contained 0.01 ± 0.00 mg/100g oil of vitamin E (α -tocopherol) and syringic acid (2.11 ± 0.03 μ g/ml). Meanwhile, the nutritional quality of defatted dabai pulp (DDP), such as total dietary fibre (TDF), total monomeric anthocyanin content (TAC), and antioxidant profile, were investigated. The amount of TDF in DDP was determined as 28.73 ± 1.82 g/100g. Whereas the amount of TAC in DDP was 523.3 ± 22.36 mg/100g. Further, HPLC analysis revealed that DDP contained gallic acid (8.73 ± 0.13 μ g/ml), 4-hydroxybenzoic acid (61.46 ± 0.04 μ g/ml), and syringic acid (89.87 ± 15.18 μ g/ml). Additionally, antioxidant assay revealed that DDP showed excellent antioxidant profile; total phenolic content (TPC): 4.404 ± 0.09 mg GAE/g extract in DDP vs 0.118 ± 0.01 mg GAE/g extract in DPO, total flavonoid content (TFC): 2.699 ± 0.01 mg QE/g extract in DDP vs 0.093 ± 0.01 mg QE/g extract in DPO, and ferric ion reducing antioxidant power (FRAP): 5.743 ± 0.01 mM Fe/g extract in DDP vs $0.87 \pm$

0.01 mM Fe/g extract in DPO. As expected, incorporation of 2% DDP in experimental diet resulted in significantly higher TPC (3.969 ± 0.01 mg GAE/g of DDP vs 3.115 ± 0.00 mg GAE/g of DPO), TFC (1.072 ± 0.00 mg QE/g of DDP vs 0.796 ± 0.00 mg QE/g of DPO) and FRAP (11.197 ± 0.01 mM Fe/g of DDP vs 9.048 ± 0.01 mM Fe/g of DPO), as compared to 2% DPO ($p < 0.05$). Further, the effectiveness of 2% of DPO and DDP was investigated against hypercholesterolemia elicited by a high-cholesterol diet in rats. Supplementation of 2% DDP and 2% DPO exerted beneficial effects against the high-cholesterol diet-fed rat. Nevertheless, results showed that 2% DDP was found to be more potent than 2% DPO in lowering TC (reduced by 35.37% in DDP vs 28.77% in DPO), LDL (reduced by 34% in DDP vs 16% in DPO), and HMG-CoA-r (reduced by 29.21% in DDP vs 18.81% in DPO) when compared with hypercholesterolemic rats ($p < 0.05$). Rats treated with 2% DDP also showed higher improvement in TAS (higher by 7.26% against DPO), SOD (higher by 7.22% against DPO), and CAT (higher by 12.71% against DPO) when compared with hypercholesterolemic rats ($p < 0.05$). Further, supplementation with 2% DDP resulted in the lowest CRP (reduced by 51.40% in DDP vs 29.90% in DPO), IL-6 (reduced by 31.20% in DDP vs 30.95% in DPO), and α -TNF (reduced by 36.12% in DDP vs 34.68% in DPO) levels compared to that of hypercholesterolemic rats ($p < 0.05$). Meanwhile, liver histology and liver function test (AST and ALT) revealed that the 2% DDP and 2% of DPO showed no toxicological significance. The cholesterol-lowering effect of 2% DDP and 2% of DPO in hypercholesterolemic rats was investigated via the ^1H NMR-based metabolomics approach. Partial Least Squares- Discriminant Analysis (PLS-DA) was employed to investigate the anti-hypercholesterolemic effect of 2% DDP and 2% of DPO and to detect related potential biomarkers. A total of seven potential biomarkers were identified in the DPO treatment model, in which citrate had the highest variable importance in the projection (VIP) value (> 3), followed by acetate, pyruvate, alanine, lysine, choline, and acetoacetate. Supplementation of 2% DPO showed a positive effect by upregulating citrate, yet the effect seen did not undergo significant changes compared with hypercholesterolemic rats ($p > 0.05$). Meanwhile, a total of nine potential biomarkers were identified in the DDP treatment model, with citrate having the highest VIP value (> 3) followed by acetate, pyruvate, choline, cis-aconitate, acetoacetate, alanine, lysine, and methylmalonate. It turned out that 2% of DDP supplementation partially recovered the dysfunction in the metabolism induced by hypercholesterolemia via lipid metabolism. The biochemical analysis and metabolomic study results revealed that 2% of DDP has better hypolipidemic activities than 2% DPO. In conclusion, SC-CO₂ extracted DDP ameliorates hypercholesterolemia by reducing TC, TG, LDL-C, and HMG-CoA-r levels. DDP also has a good effect against oxidative stress by increasing the antioxidant profile (TAS, SOD, and CAT) and reducing the inflammatory markers (CRP, α -TNF, and IL6) after 30 days of treatment. Hence, DDP is plausible to be developed as a novel source of bio-functional ingredients for the formulation of nutraceuticals. Meanwhile, the information on the quality parameters of DPO indicates the economic value of DPO to be used and commercialised as a new source of supplementary oil in the future.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia
sebagai memenuhi keperluan untuk ijazah Doktor Falsafah

**KEBERKESANAN MINYAK PULPA DABAI YANG DIEKSTRAK KARBON
DIOKSIDA LAMPAU GENTING DAN PULPA DABAI NYAHLEMAK
TERHADAP TIKUS SPRAGUE-DAWLEY HIPERKOLESTEROLEMIK
UNTUK KESIHATAN KARDIOVASKULAR**

Oleh

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Hiperkolesterolemia merupakan tanda awal kepada penyakit kardiovaskular (CVD). Penyakit ini adalah punca kematian utama di dunia. Sebanyak 17.9 juta kematian setiap tahun adalah berpunca daripada CVDs (WHO, 2017). *Canarium odontophyllum* Miq. (dabai), didapati boleh menjadi sumber baru minyak kesihatan dan bahan nutraseutikal. Kualiti parameter minyak pulpa dabai (DPO) yang telah diekstrak menggunakan teknologi karbon dioksida lampau genting (SC-CO₂) seperti kandungan kelembapan dan meruap (MVC), kandungan asid lemak bebas (FFA), nilai iodin (IV), nilai peroksida (PV) dan komposisi asid lemak (FAC) telah dikenal pasti. Kajian ini merupakan kajian pertama yang menganalisis MVC, FFA IV, dan PV dalam DPO yang diekstrak SC-CO₂. Nilai MVC DPO ialah $<0.001 \pm 0.00\%$. Seterusnya, nilai FFA DPO ialah $2.57 \pm 0.03\%$ dan nilai IV DPO ialah 53.74 ± 0.08 g iodin/100 g. Manakala, nilai PV DPO ialah 4.97 ± 0.00 mEq/kg. Komponen FAC utama DPO adalah asid palmitik ($41.56 \pm 0.10\%$), diikuti oleh asid oleik ($39.37 \pm 1.01\%$) dan asid linoleat (cis) ($12.54 \pm 1.03\%$). DPO ialah minyak yang kaya dengan asid lemak tepu (SFA) ($47.65 \pm 0.11\%$). DPO mengandungi 0.01 ± 0.00 mg / 100g vitamin E (α -tokoferol) dan asid syringik (2.11 ± 0.03 μ g/ml). Kualiti pemakanan pulpa dabai nyahlemak (DDP) seperti jumlah serabut diet (TDF), jumlah antosianin monomerik (TAC) dan profil antioksidan telah diselidik. DDP mengandungi 28.73 ± 1.82 g / 100g TDF dan 523.3 ± 22.36 mg/100g TAC. Analisis HPLC menunjukkan bahawa DDP mengandungi asid galik (8.73 ± 0.13 μ g / ml), asid 4-hidroksibenzoik (61.46 ± 0.04 μ g / ml), dan asid syringik (89.87 ± 15.18 μ g/ml). Ujian antioksidan menunjukkan bahawa DDP mempunyai profil antioksidan yang sangat baik; kandungan fenolik (TPC): 4.404 ± 0.09 mg GAE/g ekstrak DDP vs 0.118 ± 0.01 mg GAE/g ekstrak DPO, kandungan flavonoid (TFC): 2.699 ± 0.01 mg QE/g ekstrak DDP vs 0.093 ± 0.01 mg QE/g ekstrak DPO, dan kuasa pengurangan antioksidan ferik (FRAP):

5.743 ± 0.01 mM Fe/g ekstrak DDP vs 0.87 ± 0.01 mM Fe /g ekstrak DPO. Seperti yang dijangka, penambahan 2% DDP ke dalam diet eksperimen menunjukkan jumlah TPC (3.969 ± 0.01 mg GAE/g DDP vs 3.115 ± 0.00 mg GAE/g DPO), TFC (1.072 ± 0.00 mg QE/g DDP vs 0.796 ± 0.00 mg QE/g DPO) dan FRAP (11.197 ± 0.01 mM Fe/g DDP vs 9.048 ± 0.01 mM Fe/g DPO) yang lebih tinggi berbanding penambahan 2% DPO dalam diet. Keberkesanan 2% DPO dan 2% DDP telah dinilai dalam tikus diaruh hiperkolesterolemia menerusi diet berkolesterol tinggi. Penambahan 2% DPP dan 2% DPO telah menunjukkan kesan yang bermanfaat terhadap tikus dalam kajian ini. Namun, 2% DDP didapati lebih baik daripada 2% DPO dalam menurunkan TC (dikurangkan sebanyak 35.37% dalam DDP vs 28.77% dalam DPO), LDL (dikurangkan sebanyak 34% di DDP vs 16% di DPO), dan HMG-CoA-r (dikurangkan sebanyak 29.21% dalam DDP vs 18.81% dalam DPO) berbanding tikus hiperkolesterolemik ($p < 0.05$). Tikus yang dirawat dengan 2% DDP juga menunjukkan peningkatan yang lebih tinggi bagi TAS (sebanyak 7.26% vs DPO), SOD (sebanyak 7.22% vs DPO) dan CAT (sebanyak 12.71% vs DPO) berbanding tikus hiperkolesterolemik ($p < 0.05$). Penambahan 2% DDP dalam diet juga menghasilkan penurunan CRP (dikurangkan 51.40% dalam DDP vs 29.90% dalam DPO), IL-6 (dikurangkan 31.20% dalam DDP vs 30.95% dalam DPO), dan α -TNF (dikurangkan 36.12 % dalam DDP vs 34.68% dalam DPO) yang terendah berbanding tikus hiperkolesterolemik ($p < 0.05$). Keputusan histologi hati dan ujian fungsi hati (AST dan ALT) menunjukkan bahawa 2% DDP dan 2% DPO tidak membawa kepada kesan toksikologi. Selanjutnya, kesan pengurangan kolesterol pada 2% DDP dan 2% DPO terhadap tikus hiperkolesterolemik telah diselidik menggunakan pendekatan metabolomik berdasarkan resonans magnetik nukleus ($^1\text{H NMR}$). Analisis pembeza layan-kuasa dua separa terkecil (PLS-DA) telah digunakan untuk menganalisis kesan anti-hiperkolesterolemia DDP dan DPO dan mengenal pasti biopenanda berpotensi yang berkaitan. Sebanyak tujuh biopenanda berpotensi telah dikenal pasti dalam model rawatan DPO, di mana sitrat mempunyai nilai VIP tertinggi (> 3), diikuti oleh asetat, piruvat, alanin, lisin, kolin, dan asetoasetat. DPO telah berjaya menunjukkan kesan positif melalui peningkatan sitrat namun, kesan yang dilihat tidak signifikan berbanding tikus hiperkolesterolemia ($p > 0.05$). Sementara itu, sebanyak sembilan biopenanda berpotensi telah dikenal pasti dalam model rawatan DDP dengan sitrat yang mempunyai nilai VIP tertinggi (> 3) diikuti dengan asetat, piruvat, kolin, cis-asonitat, asetoasetat, alanin, lisin dan metilmalonat. DPP telah memperbaiki sebahagian daripada disfungsi metabolisme yang dipengaruhi oleh hiperkolesterolemia melalui metabolisme lipid. Analisis biokimia dan metabolomik menunjukkan bahawa 2% DDP mempunyai aktiviti hipolipidemik yang lebih baik berbanding 2% DPO. Kesimpulannya, DDP yang diekstrak SC-CO₂ mampu memperbaiki hiperkolesterolemia dengan mengurangkan kadar TC, TG, LDL-C dan HMG-CoA-r. DDP juga meningkatkan profil antioksidan (TAS, SOD dan CAT) dan mengurangkan penanda keradangan (CRP, α -TNF dan IL6) selepas 30 hari rawatan. DDP berpotensi tinggi untuk menjadi sumber bahan biofungsi untuk formulasi nutraseutikal. Sementara itu, maklumat berkaitan kualiti parameter DPO menandakan nilai ekonomi DPO yang boleh digunakan secara komersial sebagai sumber baru minyak suplemen pada masa akan datang.

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وما توفيقى الا بالله عليه توكلت واليه انيب

“And my success is not but through Allah. Upon Him, I have relied, and to Him, I return.” [Hud 11:88]

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

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LIST OF ABBREVIATIONS

4HBA	4 hydroxybenzoic acid
ABCA1	ATP-Binding Cassette Transporter
ACS	Acute Coronary Syndrome
AMI	Acute Myocardial Infarction
ARC	Agricultural Research Centre
ARIC	Atherosclerosis Risk In Communities
BW	Body Weight
CAC	Coronary Artery Calcification
CAD	Coronary Artery Disease
CHD	Coronary Heart Disease
CO ₂	Carbon Dioxide
CVD	Cardiovascular Disease
DAD	Diode-Array Detector
DDP	Defatted Dabai Pulp
DF	Dilution Factor
DPO	Dabai Pulp Oil
DPPH	2,2-Diphenyl-1-Picrylhydrazyl
ED	Endothelial Dysfunction
ELISA	Enzyme-Linked Immunosorbent Assay
FAME	Fatty Acid Methyl Esters
FH	Familial Hypercholesterolemia
FIM	Foundation for Innovation in Medicine
FRAP	Ferric Ion Reducing Antioxidant Power
g	Gram
GA	Gallic acid
GAE	Gallic Acid Equivalent
GPX	Glutathione Peroxidase
HDL-C	High-Density Lipoprotein Cholesterol
HF	Heart Failure
HMG-CoA	3-Hydroxy-3-Methylglutaryl-Coenzyme

HPLC	High-Performance Liquid Chromatography
IL	Interleukin
IVC	Individual Ventilated Cages
kcal	Kilocalorie
kg	Kilogram
LDL-C	Low-Density Lipoprotein Cholesterol
LPL	Lipoprotein Lipase
μL	Microliter
μm	Micrometer
mg	Miligram
MI	Myocardial Infarction
min	Minute
mL	Mililiter
mM	Millimolar
MOH	Ministry of Health
MPa	Megapascal Pressure
MRFIT	Multiple Risk Factor Intervention Trial
MUFA	Monounsaturated Fatty Acid
NCD	Non-Communicable Disease
NMR	Nuclear Magnetic Resonance
NPC1L1	Niemann-Pick C1-Like 1
PCA	Principle Component Analysis
PCSK9	Proprotein Convertase Subtilisin/Kexin Type 9
PLS-DA	Partial Least Squares- Discriminant Analysis
PUFA	Polyunsaturated Fatty Acid
QE	Quercetin Equivalent
rpm	Revolutions Per Minute
SA	Syringic acid
SC-CO ₂	Supercritical Carbon Dioxide
SFA	Saturated Fatty Acids
SFC	Supercritical Fluid Centre

SFE	Supercritical Fluid Extraction
SOD	Superoxide Dismutase
SREBP1	Sterol Regulatory Element-Binding Protein 1
TAS	Total Antioxidant Status
TBARS	Thiobarbituric Acid Reactive Substances
TFC	Total Flavonoid Content
TG	Triglyceride
TNF- α	Tumor Necrosis Factor α
TPC	Total Phenolic Content
TSP	Trimethylsilylpropanoic Acid
U. K	United Kingdom
VIP	Variable Importance in Projection
VLDL	Very-Low-Density Lipoprotein
VSM	Vascular Smooth Muscle

CHAPTER 1

INTRODUCTION

1.1 Background of Study

Hypercholesterolemia is the most common disorder and was reported at 39% of the worlds' adult population in 2008 (Badimon & Chiva-Blanch, 2018). In Malaysia, the latest National and Health Morbidity Survey (NHMS) 2019 reported that the prevalence of "known hypercholesterolemia" increased to 13.5% in 2019 from 9.1% in 2015. Additionally, cardiovascular disease (CVD), such as stroke and coronary heart diseases, are the leading cause of death in Malaysia (Institute for Public Health Malaysia, 2020). The Framingham Heart Study is the first to report the positive association between total cholesterol and coronary heart disease (CHD) (Kannel et al., 1971). Subsequently, the Multiple Risk Factor Intervention Trial (MRFIT) revealed a J-shaped curvilinear relationship between serum total cholesterol and CVD mortality (Stamler et al., 1986).

Later, the Johns Hopkins Precursor Study (Klag et al., 1993; Pearson et al., 1990), the Atherosclerosis Risk in Communities (ARIC) Study (Sharrett et al., 2001), Young Finns Study (Porkka et al., 1994), and the Bogalusa Heart Study (Berenson et al., 1998) subsequently confirmed that elevated serum cholesterol in young adulthood is correlated to the development of CHD later in life. Moreover, studies across different populations (The seven countries study) reveal that those with higher serum cholesterol levels showed more significant atherosclerotic burden and elevated risk of CHD events than those with lower circulating cholesterol levels (Keys et al., 1984). Hence, based on all these observations, it was widely acknowledged that high serum cholesterol elevated CHD risk, and most of these effects were attributed to the circulating level of low-density lipoprotein-cholesterol (LDL-C) (Bacchetta, 2019).

Patients tend to seek out alternative or complementary therapies for one of three reasons. First, they may dissatisfy with conventional or prescription medications that have been ineffective, harmful, too costly, or technologically oriented. Second, the selection of alternative therapies may give patients a greater sense of independence and empowerment regarding their healthcare choice. Third, and most frequently, alternative treatments are more compatible with the patient's beliefs, values, and healthcare philosophy (Astin, 1998; Poli et al., 2018). There is an opinion that public that botanical products are inherently safe because they are natural and have been used as traditional folk remedies. Little attention is paid to the lack of evidence of their efficacy or safety in well-designed controlled trials. The consumer does not consider that these products may be tainted with prescription medications or contaminated with a harmful substance, as there is a lack of regulation and standardisation

for composition, biological activity, safety, and reporting of adverse events (Marcus & Grollman, 2002; Newmaster et al., 2013). Therefore, numerous dietary supplements are taken to lower cholesterol; nevertheless, many do not demonstrate efficacy or safety in well design clinical trials and struggle with limitations as listed above. Furthermore, some patients are unable to take a pharmacological drug such as statin at appropriate doses or at all due to side effects such as myalgias. Thus, there has been a keen interest in developing novel cholesterol-lowering approaches (Rader, 2016).

Canarium odontophyllum Miq. fruit, also known as “dabai” is an indigenous seasonal fruit that can only be found in Borneo Island, especially in the Sibuan and Kapit regions of Sarawak, Malaysia. Dabai fruit is recognised as Sibuan olive due to its similar physical appearance, flavour, and texture with olive (Azlan et al., 2010). Different parts of dabai fruits demonstrated to possess antioxidant activity (Azrina et al., 2010; Chew et al., 2011; Prasad et al., 2010; Shakirin et al., 2010). Interestingly, the dabai fruit fractions (pulp and seed) possesses various biological activities such as anti-microbial (seed) (Basri, Ishak, et al., 2014), anti-fungal (pulp) (Basri, Saidi, et al., 2014), anti-Alzheimer’s (pulp and seed) (Ali-Hassan et al., 2014) and anti-hyperglycaemic (pulp) (Mokiran et al., 2014).

The potential of dabai fruit to be exploited as a new source of fruit oil was investigated in an animal model (Shakirin et al., 2012b). Supplementation of dabai pulp oil (DPO) resulted in favourable changes in blood lipid and lipid peroxidation (increased high-density lipoprotein-cholesterol (HDL-C), reduced LDL-C, triglyceride (TG), thiobarbituric acid reactive substances (TBARS) levels) with the enhancement of superoxide dismutase (SOD), glutathione peroxidase (GPx), and plasma total antioxidant status (TAS) levels in healthy rabbits (Shakirin et al., 2012b). Defatted dabai pulp (DDP) is a waste obtained from the extraction of dabai pulp oil. DDP contained anthocyanins as the major antioxidants (Khoo et al., 2012a) and 545.6 ± 2.08 g/kg of dietary fibre (Shakirin et al., 2012a). Hypercholesterolemic rabbits receiving anthocyanin-rich defatted showed cholesterol-lowering effect (reduced plasma LDL-C and total cholesterol (TC) levels) as well as reduced atherosclerotic plaques (Shakirin et al., 2012a). Moreover, the extracts of DDP have been shown to possess antioxidative properties and cardioprotective effects (Khoo et al., 2013).

1.2 Problem Statement

The key finding of NHMS 2019 revealed that CVD is the leading cause of death in Malaysia (Institute for Public Health Malaysia, 2020). The treatment and management of CVD are still a challenge to the medical system (Ozturk & Bulsara, 2012). Nevertheless, many allopathic hypolipidemic drugs are currently available on the market. They lack the desired properties such as efficacy and safety of long-term use, cost and simplicity of administration

(Davidson & Toth, 2004). These deficiencies have led to an increase in demand for cheap and affordable drugs without fewer adverse side effects. Hence, a new target for prevention and new agents for therapy with healthy benefit against elevated cholesterol need to be identified. In this context, utilisation of plants that offer lipid-lowering effect from our local natural resources (i.e., dabai) seems to be a good strategy for CVD control.

Although previous findings of solvent extracted DPO and DDP concluded both ameliorated hypercholesterolemia in rabbits, the conventional chloroform-methanol extraction could be toxic due to solvent residue of the extracted oil and waste. Supercritical fluid extraction (SFE) may offer an alternative in producing a toxic-free dabai pulp oil and defatted dabai pulp, which is plausible to be investigated as a potential source for the formulation of nutraceuticals. Therefore, this study was conducted to investigate the effectiveness of supercritical carbon dioxide (SC-CO₂) DPO and its DDP in hypercholesterolemic rats.

1.3 Significance of the Study

The utilisation of alternative green technology technique has become a hot research topic of replacing conventional extraction technique. Green extraction technology like SFE provides attractive features in overcoming the limitations of conventional extraction techniques. One of the main advantage of SFE compared to other extraction techniques; it is innocuous to human health and the environment (da Silva, Rocha-Santos, & Duarte, 2016). Due to this reason, the most extended use of SFE is in the food field (Herrero et al., 2010).

Food bioactive substances, nutraceuticals, and functional foods have become a popular topic due to increased consumer awareness and concerns about processed foods and disease risk. Consumers are actively seeking food sources and items that provide nutrition and promote and protect their health and well-being. Many of these bioactive nutrients are not available in a daily diet; henceforth, adding them in food matrices offers a great benefit to improve public health (Assadpour & Jafari, 2018). As a result, nutrition scientist should deliver the groundwork for the development of novel functional foods with the potential to provide physiological advantages or lower the long-term risk of disease onset.

Production of DPO and DDP by SC-CO₂ is still relatively new, and there are no published data available regarding the efficacies of SC-CO₂ extracted DPO and DDP in Malaysia. Consequently, the hypocholesterolemic effect of SC-CO₂ DPO and DDP in the diet-induced hypercholesterolemia rat model remains unknown. It is also crucial to understand the therapeutic mechanism of DPO and DDP using metabolomics. Metabolomics could reveal the altered metabolism in response to a treatment intervention (Chen et al., 2014).

Therefore, data generated from this study can provide useful scientific evidence of non-toxic and eco-friendly DPO and DDP extracted by SC-CO₂ as an option for the treatment of hypercholesterolemia and future application in the nutraceuticals field.

1.4 Research Objective

1.4.1 General Objective

To investigate the effectiveness of SC-CO₂ extracted DPO and DDP in hypercholesterolemic rats as a functional ingredient and source of nutraceuticals.

1.4.2 Specific Objective

1. To determine the chemical properties (moisture and volatile content, free fatty acid content, iodine value, peroxide value, and fatty acid composition), vitamin E, and antioxidant profile (total phenolic content, total flavonoid content, ferric ion reducing antioxidant power and phenolic compound) of SC-CO₂ extracted DPO.
2. To determine the nutritional quality [total monomeric anthocyanin content, total dietary fibre, and antioxidant profile (total phenolic content, total flavonoid content, ferric ion reducing antioxidant power and phenolic compounds)] of SC-CO₂ extracted DDP.
3. To determine and to compare the effect of 2% SC-CO₂ extracted DPO and 2% SC-CO₂ extracted DDP treatments on serum lipid profile, HMG-CoA reductase, and lipoprotein lipase in experimental specific pathogen-free (SPF) Sprague-Dawley rats fed with high cholesterol diet (1% cholesterol).
4. To determine and to compare the effect of 2% SC-CO₂ extracted DPO and 2% SC-CO₂ extracted DDP treatments on oxidative stress markers (MDA, TAS, SOD, GPX, and CAT) and inflammatory markers (CRP, IL-6, and α -TNF) in experimental specific pathogen-free (SPF) Sprague-Dawley rats fed with high cholesterol diet (1% cholesterol).
5. To determine and to compare toxicity effects (AST and ALT) and liver histological changes of 2% SC-CO₂ extracted DPO and 2% SC-CO₂ extracted DDP in experimental specific pathogen-free (SPF) Sprague-Dawley rats fed with high cholesterol diet (1% cholesterol).
6. To identify the potential biomarkers and metabolic alterations associated with the therapeutic effects of 2% SC-CO₂ extracted DPO and 2% SC-CO₂ extracted DDP in hypercholesterolemic rats via ¹H NMR-based metabolomics approach.

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LIST OF PUBLICATIONS

- Kadir, N.A.A.A.**, Azlan, A., Abas, F., & Ismail, I.S. (2021). Preliminary Evaluation of Supercritical Carbon Dioxide Extracted Dabai Pulp Oleoresin as a New Alternative Fat. *Molecules*, 26(18), 5545.
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