UNIVERSITI PUTRA MALAYSIA

PHENOLIC CONTENT, ANTIOXIDATIVE PROPERTIES, AND CARDIO-PROTECTIVE EFFECT OF DEFATTED DABAI EXTRACT

KHOO HOCK ENG

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By

KHOO HOCK ENG

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PHENOLIC CONTENT, ANTIOXIDATIVE PROPERTIES, AND CARDIO-PROTECTIVE EFFECT OF DEFATTED DABAI EXTRACT

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KHOO HOCK ENG

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Chair : Azrina Azlan, PhD

Faculty : Medicine and Health Sciences

Dabai (*Canarium odontophyllum* Miq) is a potential "functional fruit". This study was aimed to determine phenolics contents, antioxidant capacities, and cardio-protective effects of defatted dabai peel extract. Defatted dabai pulp and pericarp was used for comparison. This study was divided into five parts: (1) Influence of different extraction solvents on phenolic contents and antioxidant capacity of defatted dabai parts (pulp, peel, and pericarp); (2) Optimisation of phenolic extraction in defatted dabai parts using response surface methodology (RSM) and sonication-assisted extraction; (3) Evaluation of antioxidative properties of defatted dabai pulp and peel extracts prepared by solid phase extraction (SPE); (4) Determination of antioxidative and cardio-protective properties of anthocyanins from defatted dabai peel extracts; and (5) Determination of protective effects of anthocyanin-rich defatted dabai peel extracts in hypercholesterolemic rabbits based on histopathological methods (*in vivo* study). The optimised phenolic-rich crude extract of defatted dabai peel was obtained from the first and second parts of this study while anthocyanin-rich crude extract of defatted dabai peel was obtained after SPE fractionation and LCMS identification of potential phenolic compounds. The results showed that defatted dabai peel extract had the highest total phenolics and antioxidant capacity compared to the pulp extract. The total phenolic content and total anthocyanin content in the methanolic extract defatted dabai peel were 847.8 mg gallic acid equivalent (GAE)/mg extract and 0.018 µg cyanidin-3-glucoside equivalent/mg extract, respectively; while antioxidant capacity of the peel extract had 1034.8 mM TE/mg extract. Ultra high performance liquid chromatography (UHPLC) and liquid chromatography mass spectroscopy (LCMS) analyses confirmed that the defatted dabai peel extract is rich in anthocyanins (~70% of total phenolics), where cyanidin-3-glucoside (55.1 mg/g extract) was the major anthocyanin identified. *In vitro* chemical and biological assays showed that the anthocyanin-rich extract of defatted dabai peel was a strong antioxidant and had shown potent inhibitory effect against oxidative stress. The anthocyanin-rich extract had 60.1% of scavenging capacity and 1.75 mM TE/g extract as assessed by DPPH and CUPRAC assays, respectively. The

defatted dabai peel extract also had high inhibition activities (>60%) based on inhibition of CD36 and PARP-1 ELISA. The results from biological assays also demonstrated that the anthocyanin-rich extract had significantly lower TBARS values as compared to positive control. For *in vivo* study, three doses of defatted dabai peel extract (1000, 2000, and 3000 mg per day) obtained from RSM optimisation and sonication-assisted extraction were supplemented to hypercholesterolemic rabbits for eight weeks. The results revealed that the defatted dabai peel extract is a potential cardio-protective agent, where high dose supplementation reduced severity of hepatic fibrosis, decreased severity of steatosis in kidney, and lessened the degrees of inflammation or atherosclerotic plaques formation in the aorta and right ventricle of the heart of the hypercholesterolemic rabbits. Therefore, defatted dabai peel is a potential source of nutraceutical ingredient for cardio-protection.

Abstrak tesis yang dikemukan kepada Senat Universiti Putra Malaysia
Sebagai memenuhi keperluan untuk ijazah Doktor Falsafah

KANDUNGAN FENOLIK, CIRI ANTIOKSIDATIF DAN KESAN PERLINDUNGAN UNTUK JANTUNG DARIPADA EKSTRAK DABAI NYAHLEMAK

Oleh

KHOO HOCK ENG

Februari 2014

Pengerusi : Azrina binti Azlan, PhD

Fakulti : Perubatan dan Sains Kesihatan

Dabai (*Canarium odontophyllum* Miq) adalah sejenis buah berpotensi sebagai "buah fungsian". Kajian ini bertujuan untuk menentukan kandungan fenolik, kapasiti antioksidan dan kesan perlindungan kesihatan jantung daripada ekstrak kulit dabai nyahlemak. Isi dan perikarp dabai nyahlemak telah digunakan sebagai perbandingan. Kajian ini dibahagikan kepada lima bahagian: (1) Pengaruh pelbagai pelarut pengekstrakan terhadap kandungan fenolik dan kapasiti antioksidan daripada bahagian buah dabai nyahlemak (isi, kulit dan pericarp); (2) Pengoptimuman pengekstrakan fenolik dalam bahagian dabai nyahlemak dengan menggunakan Keadah Permukaan Gerak Balas (KPGB) dan pengekstrakan bantuan-sonikasi; (3) Penilaian ciri antioksidan ekstrak isi dan kulit dabai nyahlemak yang disediakan melalui pengekstrakan fasa pepejal (PFP); (4) Penentuan ciri antosianin, antioksidatif dan perlindungan untuk jantung daripada ekstrak kulit dabai nyahlemak; dan (5) Penentuan kesan perlindungan daripada ekstrak kulit dabai nyahlemak kaya antosianin dalam arnab berkolesterol tinggi berdasarkan kaedah histopatologi (kajian *in vivo*). Ekstrak mentah kaya fenolik dioptimumkan telah didapati daripada kulit dabai nyahlemak daripada bahagian pertama dan kedua kajian ini, manakala ekstrak antosianin kulit dabai nyahlemak adalah didapati selepas pemeringkatan PFP dan penentuan potensi sebatian fenolik menggunakan kromatografi cecair spektrometri jisim (LCMS). Keputusan kajian menunjukan bahawa ekstrak kulit dabai nyahlemak mengandungi jumlah fenolik dan kapasiti antioksidan tertinggi berbanding ekstrak isinya. Kandungan jumlah fenolik dan kandungan jumlah antosianin dalam ekstrak metanol kulit dabai nyahlemak adalah 847.8 mg setara asid galik (GAE)/mg ekstrak dan 0.018 µg setara sianidin-3-glukosida/mg ekstrak masing-masing. Analisa kromatografi cecair prestasi ultra tinggi (UHPLC) dan kromatografi cecair spektrometri jisim mengesahkan bahawa ekstrak kulit dabai nyahlemak adalah kaya dengan antosianin (~70% jumlah fenolik), di mana sianidin-3-glukosida (55.1 mg/g ekstrak) merupakan antosianin utama. Esei *in vitro* kimia dan biologi membuktikan bahawa ekstrak yang kaya dengan antosianin daripada kulit dabai

nyahlemak mengandungi antioksidan yang kuat dan menunjukkan kesan rencatan yang mujarab terhadap tegasan oksidatif. Ekstrak kaya antosianin menunjukkan 60.1% kapasiti hapus-sisa dan 1.75 mM setara Trolox/g ekstrak berdasarkan esei DPPH dan CUPRAC masing-masing. Ekstrak kulit dabai nyahlemak juga menunjukkan aktiviti perencatan yang tinggi (>60%) melalui kaedah ELISA perencatan CD36 dan PARP-1. Keputusan kajian daripada esei biologi juga menunjukkan bahawa ekstrak kaya antosianin menunjukkan nilai TBARS yang jauh lebih rendah berbanding kawalan positif. Bagi kajian *in vivo*, tiga dos ekstrak kulit dabai nyahlemak (1000, 2000 dan 3000 mg sehari) hasil daripada pengoptimuman dengan Kaedah Permukaan Gerak Balas dan pengekstrakan bantuan-sonikasi telah diberikan kepada arnab berkolesterol tinggi selama 8 minggu. Keputusan kajian itu menunjukkan ekstrak mentah kulit dabai nyahlemak berpotensi sebagai agen perlindungan jantung, di mana pemberian ekstrak dos tinggi (3000 mg dalam satu hari) mengurangkan tahap fibrosis pada hati, mengurangkan tahap steatosis pada ginjal dan mengurangkan tahap kebengkakan atau pembentukan plak aterosklerotik dalam aorta dan ventrikal jantung kiri arnab berkolesterol tinggi itu. Oleh itu, kulit dabai nyahlemak adalah satu sumber kepada ramuan nutraseutikal yang berpotential untuk perlindungan jantung.

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I certify that a Thesis Examination Committee has met on 24 February 2014 to conduct the final examination of Khoo Hock Eng on his thesis entitled "Phenolic Content, Antioxidative Properties, and Cardio-protective Effect of Defatted Dabai Extract" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the Doctor of Philosophy.

Members of the Thesis Examination Committee were as follows:

Asmah Rahmat, PhD
Professor
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Chairman)

Norhaizan Mohd Esa, PhD
Associate Professor
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Internal Examiner)

Tan Chin Ping, PhD
Professor
Faculty of Food Science and Technology
Universiti Putra Malaysia
(Internal Examiner)

Kalidas Shetty, PhD
Professor
North Dakota State University
USA
(External Examiner)

_____

NORITAH OMAR, PhD
Associate Professor and Deputy Dean
School of Graduate Studies
Universiti Putra Malaysia

Date: 21 April 2014

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

Azrina Azlan, PhD
Associate Professor
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Chairperson)

Amin Ismail, PhD
Professor
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Member)

Faridah Abas, PhD
Associate Professor
Faculty of Food Science and Technology
Universiti Putra Malaysia
(Member)

Muhajir Hamid, PhD
Associate Professor
Faculty of Biotechnology and Biomolecular Sciences
Universiti Putra Malaysia
(Member)

BUJANG BIN KIM HUAT, PhD
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Signature:	_____	Signature:	_____
Name of Chairman of Supervisory Committee:	Associate Professor Dr. Azrina Azlan	Name of Member of Supervisory Committee:	Professor Dr. Amin Ismail
Signature:	_____	Signature:	_____
Name of Member of Supervisory Committee:	Associate Professor Dr. Faridah Abas	Name of Member of Supervisory Committee:	Associate Professor Dr. Muhajir Hamid

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LIST OF ABBREVIATIONS

ABTS	2,2′-azinobis-(3-ethylbenzothiazoline-6-sulfonate)
ANOVA	Analysis of variance
AR	Analytical reagent
AS	Anthocyanidin synthase
BSA	Bovine serum albumin
BW	Body weight
C3A	Cyanidin-3-arabinoside
C3G	Cyanidin-3-glucoside
C3L	Cyanidin-3-galactoside
C3R	Cyanidin-3-rutinoside
CCD	Central composite design
CD36	Cluster of differentiation 36
CDL	Curved desolvation line
CN	Cyanopropyl
CO	*Canarium odontophyllum*
COX-2	Cyclooxygenase-2
CUPRAC	Copper (II) reduction antioxidant capacity
CVD	Cardiovascular disease
DAD	Diode array detector
DF4R	Dihydroflavonol 4-reductase
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
DPPH	2,2-Diphenyl-1-picrylhydrazyl
DTT	1,4-dithiothreitol
DW	Dry weight
EDTA	Ethylenediaminetetraacetic acid
ELISA	Enzyme-linked immunosorbent assay
ET	Electron-transfer
EtOH	Ethanol
F3’H	Flavonoid 3'-hydroxylase
FRAP	Ferric-reducing antioxidant power
FW	Fresh weight
GAE	Gallic acid equivalent
H & E	Haematoxylin and eosin
HAT	Hydrogen atom transfer
HCl	Hydrochloric acid
HDL	High-density lipoprotein
HDL-c	High-density lipoprotein-cholesterol
HH	Hypercholesterolemic high dose extract
HL	Hypercholesterolemic low dose extract
HM	Hypercholesterolemic medium dose extract
HNE	4-hydroxynonenal
HPLC	High-performance liquid chromatography
HS	Hypercholesterolemic statin group

HUVEC	Human umbilical vein endothelial cells
IC_{50}	Inhibition concentration (50%)
ICAM-1	Intercellular adhesion molecule 1
INOS	Inducible nitric oxide synthase
L3G	Pelargonidin-3-glucoside
LC	Liquid chromatography
LC-MS	Liquid chromatography-mass spectrometry
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LDL-c	Low-density lipoprotein-cholesterol
LOD	Limit of detection
LOQ	Limit of quantitation
M3G	Malvidin-3-glucoside
MDA	Malonaldehyde
MeOH	Methanol
MS	Mass spectroscopy
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide
N3H	Naringenin 3-hydrolase
NAD	Nicotinamide adenine dinucleotide
NC	Negative control
ND	Not detected
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NO	Nitric oxide
oxLDL	Oxidised LDL
P3G	Peonidin-3-glucoside
PARP	Poly(ADP-ribose) polymerase
PBS	Phosphate buffer saline
PC	Positive control
PDA	Photodiode array
PP	Pericarp
RBC	Red blood cell
RSM	Response surface methodology
RNS	Reactive nitrogen species
ROS	Reactive oxygen species
RSD	Relative standard deviation
SD	Standard deviation
SPE	Solid phase extraction
TAC	Total anthocyanin content
TAS	Total antioxidant status
TBA	Thiobarbituric acid
TBARS	Thiobarbituric acid reactive substances
t-BHP	*tert*-Butyl hydroperoxide
TCA	Trichloroacetic acid
TEAC	Trolox equivalent antioxidant capacity
TFA	Trifluoroacetic acid
TFC	Total flavonoid content

TMB	3,3',5,5'-Tetramethylbenzidine
TPC	Total phenolic content
TPTZ	2,4,6-tris(2-pyridyl)-striazine
UF3GT	Uridine diphosphate glucose flavonoid 3-O-glucosyltransferase
UHPLC	Ultra-high performance liquid chromatography
UPM	Universiti Putra Malaysia
UV	Ultra-violet
VLDL	Very low-density lipoprotein

LIST OF NOTATIONS

$ABTS^{\bullet}$	ABTS radical
CO_2	carbon dioxide
$CuCl_2$	copper (II) chloride
$CuSO_4$	copper sulphate
Fe(II)	iron 2+
Fe(III)	iron 3+
HEK 293	human embryonic kidney cell line
HL-60	human promyelocytic leukemia cell line
H_2O	water
H_2O_2	hydrogen peroxide
HO·	hydroxyl radical
Na_2CO_3	sodium bicarbonate
NaN_3	sodium azide
$^1O_2$	singlet oxygen
$\cdot O_2^-$	superoxide
−OH	hydroxyl group
ROOR'	various peroxides
ROOH	hydroperoxides
SH-SY5Y	human neuroblastoma cell line
SO_2	sulfur dioxide
Trolox	6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid
v/v	volume/volume
w/w	weight/weight

CHAPTER 1

INTRODUCTION

1.1. Research Background

Fruit of *Canarium odontophyllum* Miq., locally known as dabai is a dark purple-coloured fruit when ripe. It is from Burseraceae family of the plant kingdom. Dabai tree is specifically grown largely in BorneoIsland, especially Sarawak. In Malaysia, dabai fruit is identified based on the herbarium voucher specimens (S 40073-Niah; S 64872-Kapit; S 73759-Tebedu), and it is locally known as Sibu olive. Dabai has oily and juicy pulp with a hard 3 angular seed in it. It has high fat content where the fat is ~25% (Chew et al., 2011). The saturated fat content of dabai oil (44%) is similar as in palm oil (47%). Nutritional composition (Chew et al., 2011) and physicochemical characteristics (Azrina et al., 2010a; Ding & Tee, 2011) of dabai had been studied since past few years.

Dabai contains high phenolics, where high phenolic content has also been determined in olive since past few decades (Lesage-Meessen et al., 2001; Marsilio et al., 2001). High total phenolic content (TPC) has been reported in dabai parts, especially in peel, pulp and seed. The highest TPC has been found in water extract of dabai peel [18 mg gallic acid equivalent (GAE)/g fresh weight (FW)], followed by pulp (5 mg GAE/g FW) and seed (3 mg GAE/g FW) (Prasad et al., 2010). Besides, dabai fruit has similar characteristic to olive, such as fat with high total phenolic content (Azrina et al., 2010a). As dabai has high TPC, the phenolic compounds extracted from dabai are very useful for health maintenance particularly in prevention of cardiovascular diseases (CVD).

Previous studies have looked at different parts of dabai in terms of its nutritional composition, such as proximate contents, vitamins, minerals, polyphenolic compounds, carotenoids and antioxidant activities (Chew, 2011; Prasad et al., 2010; Prasad et al., 2011; Shakirin, 2011). Dabai fruit has been reported to contain high antioxidant activity, especially in its peel (Azrina et al., 2010). Several *in vitro* antioxidant assays such as DPPH, FRAP, TEAC, and β-carotene bleaching assays had been used in the determination of antioxidant activities (capacities) in dabai extracts. According to Prasad et al. (2010), using four antioxidant assays, dabai peel extracts had the highest antioxidant activities, followed by pulp and kernel extracts. Based on DPPH, FRAP and β-carotene bleaching assays, methanolic extract of dabai peel had the highest antioxidant activities, followed by pulp and kernel (Azrina et al., 2010). The high antioxidant activity of the dabai parts is possibly due to the high amount of phenolic compounds such as phenolic acids, flavonoids and anthocyanins (Chew, 2011).

Dabai contains 25% of fat. The fatty acid composition of dabai fat has been well characterised (Azrina et al., 2010a). As a high fat fruit, direct consumption of dabai fruit in big amount may lead to excessive of energy intake. Previous studies also have found that dabai oil has a beneficial effect to human health (Shakirin et al., 2010; Shakirin et al., 2012a,b). The oil had also been studied since past few years by local researchers

(Azrina et al., 2010a; Azrina & Ismail, 2011). Extracting oil has resulted in defatted parts of dabai that is purple in colour and rich in antioxidant. There is a need to study the defatted pericarp, especially the peel as purple powder. By-product of dabai oil extraction gives rise to defatted dabai parts that are purple in colour.

Defatted dabai is another alternative source to obtain phenolic compounds for prevention of CVD. Extraction of dabai oil has yielded defatted dabai parts (peel and pulp). As the by-products of dabai oil extraction, it is worth to determine the antioxidant capacity and cardio-protective capacity of the by-products. Previous study has explored the potential health benefits of different dabai parts. Shakirin (2011) reported that supplementation of dabai oils and different parts (pericarp and peel) of dabai have shown beneficial effects in reducing risks of CVD by increasing plasma high-density lipoprotein (HDL) level and total antioxidant status, by reducing low-density lipoprotein (LDL) level, and by suppressing lipid peroxidation in hypercholesterolemic rabbits. Therefore, dabai is rich in medicinal properties, especially its pulp and peel.

Defatted parts of dabai have a higher level of polar phenolics compared with dabai oil. However, previous studies did not determine the bioactive components of dabai especially in the defatted parts. Due to the high cost of medicine to treat CVD plus the potential of these bioactive compounds against CVD, it is worth to characterise bioactive components of the defatted dabai as a new source of active compounds for nutraceutical or pharmaceutical properties.

1.2. Problem Statements

CVDs are typical metabolic diseases affecting health of the world population. These diseases have a rising cost for treatment with increasing price of medicine and health care services. Despite the aggressive efforts put by various research groups and the government sector, there is still increasing prevalence of CVD year after year. In year 2006, 80 million of the American adults (one in three) have affected by CVD while 38.1 million of them were ≥60 year-old (AHA, 2009).In Malaysia, the prevalence of CVD was increasing, especially in the urban areas. Women are known to develop CVD about 10 years later than men (Lim, 2009). In year 2007, CVD was the main cause of death in Malaysia (Jabatan Perangkaan Malaysia, 2009). Currently, CVD has become the most common death cases in Malaysia. Besides, the fourth National Health and Morbidity Survey 2011 revealed about 90% of CVD risk was attributed by unhealthy lifestyle, and obese individual has an increasing risk of CVD (Choo, 2012).

CVDs are closely associated with hypertension, arteriosclerosis, and hyperlipidemia (Leiro & Martín, 2006). These diseases are commonly experienced by people with unhealthy lifestyle, stress and physical inactivity. The potential cause of CVD is oxidative stress (Fearon & Faux, 2009). Tapia et al. (1999) reported that oxidative stress has contributed to lipid peroxidation. However, the underlying mechanism is unclear. Persson et al. (2007) suggested that elevated level of plasma LDL has linked to increase the risk of arteriosclerosis. Besides that, liver also plays an important role in the regulation of lipoproteins (Lima et al., 2006). The catabolism of LDL is regulated by

LDL receptors in the liver, where the LDL receptor formed due to an excessive level of plasma cholesterol. Impaired LDL catabolism is occurred during increasing oxidative stress condition, resulted in oxidative damage and LDL peroxidation (Dashti et al., 1984). Oxidised LDL will further exacerbate the atherosclerotic lesion formation by several pathways (Heinecke, 1999).

Studies have indicated that elevated level of LDL is the primary risk factor for CVD (Pekkanen et al., 1989; Persson et al., 2007; AHA, 2009). Other plasma lipids and lipoproteins such as triglyceride, high-density lipoprotein (HDL) and very low density lipoprotein (VLDL) have been demonstrated to be significant and independent risk factors for CVD (Despres et al., 1990). Other risk factors for promotion of CVD had been recognised, including diabetes, cigarette smoking, low estrogen level in post-menopausal women and elevated homocysteine level (Castelao & Gago-Dominguez, 2008). LDL oxidation is closely related to the development of CVD, and oxidative stress is the primary cause of LDL oxidation. Oxidative stress had been recognised to be resulted from increased in the cellular level of reactive oxygen species, which will eventually cause cell death (Lima et al., 2006). To prevent the oxidation of cellular lipoproteins, dietary antioxidants act as free radical scavengers, delay cell proliferation and DNA damage that will result in cell death (Vitaglione et al., 2005).

Statin is widely used in prevention of CVD. Heavy use of statin is of great health concern. The use of statin in lowering lipid is related to hepatotoxicity due to elevated liver enzymes in statin-treated patients (Dourakis, 2006). So as to minimise the side effects of synthetic drugs used in prevention of CVD, potent natural sources of nutraceutical are recommended to replace the used of synthetic drugs. Fruits are good sources for nutraceutical and pharmaceutical ingredients. Dark coloured fruits are rich in antioxidants especially the polyphenolic compounds. Among the studied fruits, Cieślik et al. (2006) reported that European elder (elderberry) had the highest polyphenol content, followed by pink grapefruit, kiwi fruit, plum and orange. The study also revealed that polyphenol content of European elder, pink grapefruit and kiwi were more than two times higher than in the selected vegetables, such as broccoli, cabbage, carrot and tomato. Polyphenolic content of apple was also studied by Paganga et al. (1999) and showed a high antioxidant activity as assessed using Trolox equivalents assay. Chew et al. (2012) reported that dabai fruit contained high phenolic compounds. As dabai fruit is a potential source of nutraceutical ingredient, anthocyanin-rich defatted dabai peel as a by-product of dabai oil extraction should potentially be promoted as a natural source for prevention of diseases.

Bioavailability of anthocyanin could be another issue. Anthocyanin is commonly known to have low bioavailability due to its molecular structure, and the special characteristic in solutions with different pH. A possible reason for the low bioavailability is mainly due to the increasing rate of cellular uptake and excretion (Faria et al., 2013). Manach et al. (2005) revealed that plasma concentration of anthocyanin was the lowest if compared with plasma concentrations of flavonoids and flavanones after ingestion of these antioxidants-rich foods; however, high urinary excretion of anthocyanin (as high as 7% of the anthocyanin intake) was found from the

study. In human, most of the anthocyanins consumed were found as metabolites and anthocyanin-derivatives (Vitaglione et al., 2007; Faria et al., 2013). Therefore, low amount of anthocyanins found in human plasma does not mean that the anthocyanins have poor bioavailability.

Up to this date, no study has been carried out on identification and confirmation of phenolic compounds in defatted dabai parts. In order to be served as a source for nutraceuticals and pharmaceuticals, characterisation of individual phenolic compounds using LCMS/MS is needed to provide a description of phenolic compounds in dabai. Existing procedures for optimisation of polyphenol extraction and identification are adequate, but, not for dabai fruit. Therefore, optimisation of extraction method is needed. Hence, determination of total phenolics and individual phenolic compounds in dabai, especially the defatted portions are essential for future referencing.

Defatted dabai peel could be used as a potent functional food or nutraceutical ingredient. Determination of antioxidant capacity and cardio-protective effect in defatted dabai peel using antioxidant assays and bioassays may help to establish a link between antioxidant properties of defatted dabai peel and cardio-protection. Therefore, fractionation and quantification of potential anthocyanin compounds in the defatted dabai peel are essential as anthocyanin could be one of the major bioactive compounds with cardio-protective effect. More scientific evidences are needed for cardio-protective effects of bioactive compounds extracted from defatted dabai peel.

1.3. Significant of the Study

Currently, natural products have been used as sources of pharmaceutical ingredients; therefore, the side effects caused by the use of synthetic drugs will be no longer a serious issue. The use of natural products as nutraceutical and pharmaceutical ingredients has replaced drug prescription in prevention of CVD. Increasing number of nutraceutical supplements can be seen selling in pharmacies. Dabai pulp oil has TPC of 202.7 mg GAE/kg oil while dabai kernel oil has TPC of 39.4 mg GAE/kg oil (Shakirin et al., 2012b). The TPC was shown to highly correlate with antioxidant activities as assessed using electron transfer and hydrogen atom transfer reaction assays (Azrina et al., 2010). As mentioned earlier, defatted pericarp of dabai resulted from oil extraction should contain a high amount of phenolic compounds. Phenolic compounds can be categorised as polar and non-polar forms. The phenolics of defatted dabai parts can be categorised as polar form as most of the non-polar phenolics should have been removed during oil extraction.

Polar and semi-polar phenolics, such as phenolic acids, flavonoids and anthocyanins are remained in the defatted dabai pulp. The purple-coloured peel of dabai is also a rich source of anthocyanin. The phenolic compounds in the defatted dabai pulp and peel are postulated to have high antioxidant capacity. The phenolic compounds are also potential cardio-protective agents (Hertog, 1996). Anthocyanins as one of the major bioactive compounds determined in dabai fruit, especially in the peel (Chew et al., 2012) have beneficial effects to human health, especially reduce the risk of CVD (Shakirin, 2011).

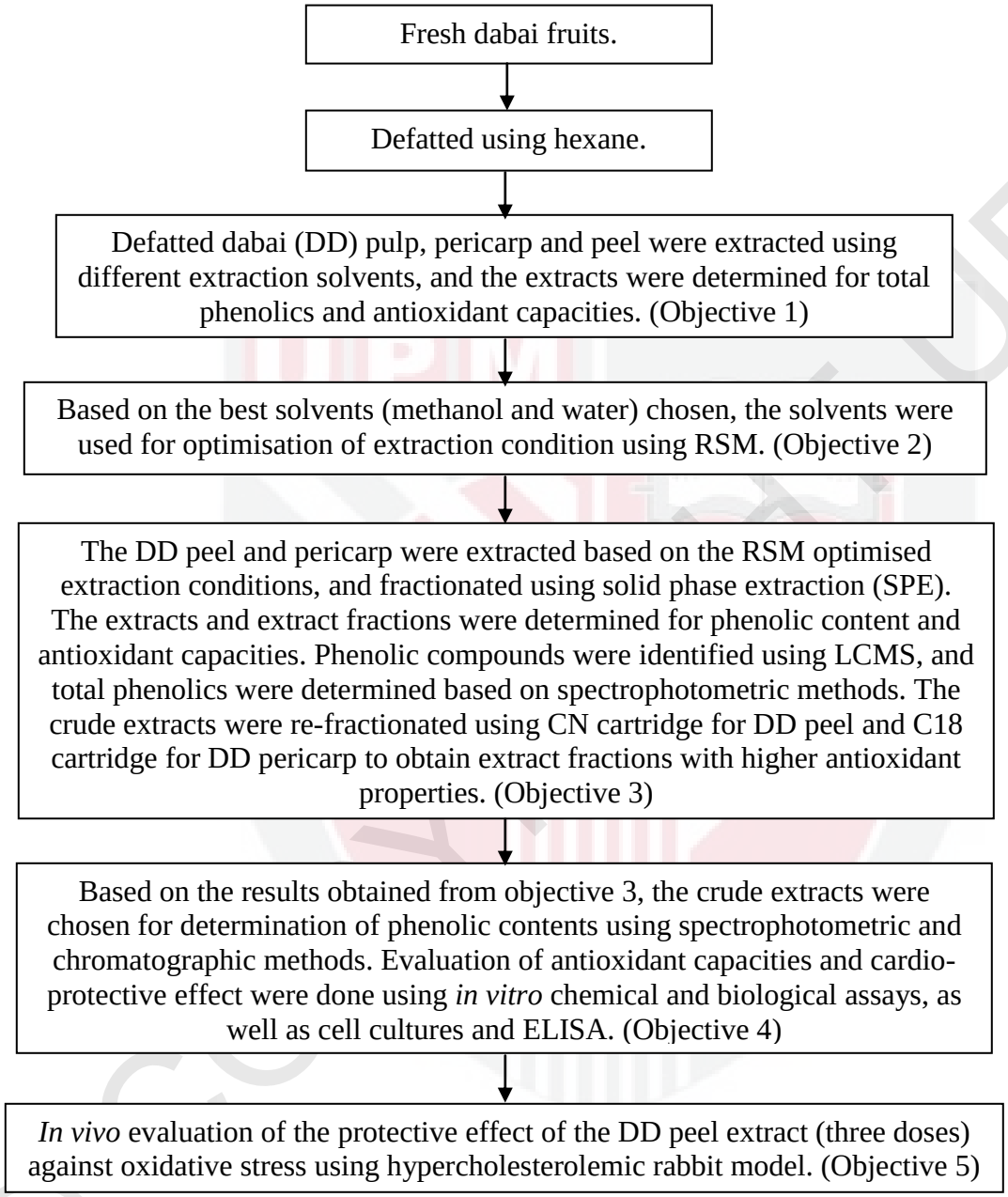
Previously, anthocyanins in boysenberry and blackcurrant had shown to prevent hydrogen peroxide-induced oxidative damages in human neuroblastoma (SH-SY5Y) and promyelocytic (HL-60) cells (Ghosh et al., 2006). Besides, Wallace (2011) also revealed that dietary anthocyanins have promising cardio-protective effects. On the other hand, dabai peel is a potential source of antioxidant. Dabai peel has high TPC [387.5 ± 33.23 mg GAE/100 g FW] and antioxidant activity, but the TPC of dabai pulp and kernel were lower 267.0 ± 4.24 and 51.0 ± 0.01 mg GAE/100 g FW when compared with the peel (Azrina et al., 2010). Tripoli et al. (2005) also reported that olive fruit (have same characteristic with dabai) contained numerous substances of phenols.

Based on information from previous studies, defatted dabai powder is known as a potent source of nutraceutical for lipid lowering, such as lowering plasma triglyceride, total cholesterol and LDL levels, and increasing plasma HDL level in New Zealand white rabbits (Shakirin et al., 2012a). The defatted dabai parts also reduced plasma lipid peroxidation marker and increased total antioxidant status of the animals. Therefore, there is a need to detect, fractionate, and quantify the potential polyphenolic compounds in defatted dabai parts, especially the peel. The specific compound or group of compound identified can be used as active pharmaceutical ingredient or as nutraceutical in future. There is also a need to confirm the antioxidative and cardio-protective effects of the defatted dabai peel using *in vitro* and *in vivo* assays. Hypercholesterolemic animal model should be performed to further confirm the cardio-protective effect of anthocyanin-rich crude extract of defatted dabai peel.

1.4. Study Objectives

1. To compare antioxidant contents (total phenolic content, total flavonoid content and total anthocyanin content) and antioxidant capacities of defatted dabai parts by different extraction solvents (as crude extracts)
2. To optimise extraction conditions of crude extracts of defatted dabai parts using response surface methodology
3. To fractionate antioxidative compounds of the optimised crude extracts of defatted dabai peel using solid phase extraction
4. To evaluate the antioxidative properties and cardio-protective effects of the optimised anthocyanin-rich extract of defatted dabai peel using *in vitro* chemical assays and bioassays
5. To determine the potential protective effects of the optimised anthocyanin-rich extracts of defatted dabai peel in hypercholesterolemic rabbits model

1.5. Flow Chart of the Study



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