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CHOLESTEROL-LOWERING PROPERTIES OF DEFATTED KENAF SEED MEAL AND ITS PHENOLICS-SAPONINS-RICH EXTRACT IN A RAT MODEL

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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 Doctor of Philosophy

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CHOLESTEROL-LOWERING PROPERTIES OF DEFATTED KENAF SEED MEAL AND ITS PHENOLICS-SAPONINS-RICH EXTRACT IN A RAT MODEL

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Kenaf (*Hibiscus cannabinus* L.) is an important commercial fiber crop and defatted kenaf seed meal (DKSM) is a secondary by-product from the kenaf industry. The present study focused on the investigation of cholesterol-lowering properties of DKSM and its phenolics-saponins-rich extract (PSRE) in a rat model. Proximate analysis revealed that DKSM was high in protein, carbohydrate and crude fibre; while magnesium, potassium and phosphorus were the major minerals found in DKSM. The absence of acute oral toxicity in DKSM was observed through brine shrimp and rat models. In addition, DKSM exhibited higher phenolic content and antioxidant activity as compared to the selected edible flours ($p < 0.05$). Next, PSRE was prepared from refluxed extraction of DKSM and then fractionated with n-butanol to obtain butanolic (BF) and aqueous (AqF) fractions, which were respectively rich and deficient in phenolic-saponin content. BF was confirmed to exhibit the highest phenolic-saponin content and antioxidant activity, followed by PSRE and AqF ($p < 0.05$). Antioxidant activity of PSRE and its fractions were strongly correlated to their phenolic-saponin content, suggesting that phenolics and saponins may be the key bioactives that contribute to the antioxidant properties of DKSM and PSRE. Cholesterol-lowering properties of DKSM and PSRE were evaluated through a hypercholesterolemic rat model and dietary interventions were conducted by incorporating DKSM (15% and 30% of total diet) or PSRE (at 2.3% and 4.6% of total diet, respectively equivalent to the total content of DKSM-phenolics and saponins in the DKSM groups) into the atherogenic diets. After 10 weeks of DKSM and PSRE supplementation, the hepatosomatic index, hepatosteatosis, serum lipid profile, Castelli risk indexes and toxicity biomarkers of hypercholesterolemic rats were significantly improved ($p < 0.05$). Besides, the levels of hepatic Hmgcr and serum Pcsk9 were lowered, along with transcriptional upregulations of hepatic Cyp7a1, Abca1, Lcat, ApoA2 and ApoE ($p < 0.05$). The gene expression of hepatic Ldlr was insignificantly enhanced by

DKSM ($p > 0.05$), but significantly upregulated by PSRE ($p < 0.05$). The combined results showed that hypercholesterolemia and atherogenic risk in rats were effectively attenuated by DKSM and PSRE supplementation, possibly via modulations of multiple vital processes in hepatic cholesterol metabolism. In addition, serum total antioxidant capacity and hepatic expression of antioxidant genes of hypercholesterolemic rats were significantly enhanced by DKSM and PSRE supplementation, accompanied with marked suppression against the levels of circulating oxidized low-density lipoprotein and pro-inflammatory biomarkers ($p < 0.05$). Apart from the potential beneficiary effects of alleviated hypercholesterolemia, DKSM and PSRE may attenuate hypercholesterolemia-associated oxidative stress and systemic inflammation in rats by enhancing the serum total antioxidant capacity as well as the endogenous antioxidant defense via activation of hepatic Nrf2-ARE pathway. In conclusion, DKSM and its-derived PSRE are effective functional food ingredients in ameliorating hypercholesterolemia and its-associated oxidative stress and systemic inflammation in the rat model. Phenolics and saponins may be the bioactives conferring DKSM and PSRE with their cholesterol-lowering, antioxidative and anti-inflammatory properties.

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CIRI-CIRI PENURUNAN KOLESTEROL BAGI TEPUNG BIJI KENAF NYAHLEMAK DAN EKSTRAK KAYA FENOLIK-SAPONINNYA DALAM MODEL TIKUS

Oleh

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Kenaf (*Hibiscus cannabinus* L.) adalah sejenis tanaman serat komersil yang utama dan tepung biji kenaf nyahlemak (DKSM) merupakan produk sampingan sekunder daripada industri kenaf. Kajian ini memberi tumpuan kepada penilaian ciri-ciri penurunan kolesterol bagi DKSM dan ekstrak kaya fenolik-saponinnya (PSRE) dalam model tikus. Analisis proksimat menunjukkan bahawa DKSM mempunyai kandungan protein, karbohidrat dan serat kasar yang tinggi, manakala magnesium, kalium dan fosforus merupakan mineral utama bagi DKSM. DKSM tidak menunjukkan ketoksikan oral akut melalui model udang brin dan tikus. Tambahan pula, DKSM menunjukkan kandungan fenolik dan aktiviti antioksidan yang lebih tinggi daripada tepung makanan terpilih ($p < 0.05$). Seterusnya, PSRE disediakan daripada DKSM melalui pengekstrakan refluks dan difraksikan kepada fraksi butanol (BF) dan akues (AqF) yang masing-masing kaya dan kekurangan dalam kandungan fenolik-saponin. BF telah disahkan mempunyai kandungan fenolik-saponin dan menunjukkan aktiviti antioksidan yang tertinggi, diikut oleh PSRE dan AqF ($p < 0.05$). Aktiviti antioksidan bagi PSRE dan fraksi-fraksinya didapati berkorelasi baik dengan kandungan fenolik-saponinnya dan ini mencadangkan kemungkinan bahawa fenolik dan saponin adalah sebatian bioaktif utama yang menyumbang kepada aktiviti antioksidan DKSM dan PSRE. Ciri-ciri penurunan kolesterol bagi DKSM dan PSRE telah dinilai melalui model tikus hiperkolesterolemia dan intervensi diet dijalankan dengan memasukkan DKSM (15% dan 30% dari jumlah diet) atau PSRE (2.3% and 4.6% dari jumlah diet, masing-masing setara dengan fenolik dan saponin jumlah DKSM yang terkandung dalam kedua-dua kumpulan DKSM) ke dalam diet aterogenik. Sepuluh minggu selepas suplementasi DKSM and PSRE, indeks hepatosomatik, hepatosteatosis, profil lipid serum, indeks risiko Castelli dan biopenanda ketoksikan bagi tikus hiperkolesterolemia diperbaiki secara signifikan ($p < 0.05$). Selain itu, tahap Hmgcr hepatik dan Pcsk9 serum telah

diturunkan, bersama-sama dengan peningkatan kawalatur transkripsi hepatik bagi Cyp7a1, Abca1, Lcat, ApoA2 and ApoE ($p < 0.05$). Ekspresi gen bagi Ldlr hepatik dipertingkatkan secara tidak signifikan oleh DKSM ($p > 0.05$), tetapi secara signifikan oleh PSRE ($p < 0.05$). Gabungan daripada semua penemuan ini menunjukkan bahawa hiperkolesterolemia dan risiko aterogenik dalam tikus telah direncatkan secara efektif oleh suplementatsi DKSM dan PSRE, berkemungkinan melalui modulasi pelbagai proses utama dalam metabolisme kolesterol hepatik. Di samping itu, kapasiti antioksidan, jumlah serum dan ekspresi gen antioksidan hepatik bagi tikus hiperkolesterolemia dipertingkatkan secara signifikan oleh suplementasi DKSM dan PSRE, bersama-sama dengan perencatan yang ketara terhadap tahap lipoprotein ketumpatan rendah teroksida dan biopenanda pro-radang edaran ($p < 0.05$). Selain daripada kesan manfaat daripada perencatan hiperkolesterolemia, DKSM and PSRE mungkin mengurangkan tekanan oksidatif dan keradangan sistemik yang berkaitan dengan hiperkolesterolemia dalam tikus dengan penambahbaikan kapasiti antioksidan jumlah serum dan peningkatan pertahanan antioksidan dalaman melalui pengaktifan laluan Nrf2-ARE hepatik. Kesimpulannya, DKSM dan terbitan PSRE merupakan ingredien makanan berfungsi yang berkesan dalam mengurangkan hiperkolesterolemia serta tekanan oksidatif dan keradangan sistemik yang berkaitan dengannya dalam model tikus. Fenolik dan saponin dicadangkan sebagai sebatian bioaktif yang menyumbang kepada ciri-ciri penurunan kolesterol, antipengoksidaan dan anti-keradangan bagi DKSM dan PSRE.

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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 degree of Doctor of Philosophy. The members of the Supervisory Committee were as follows:

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·OH	Hydroxyl radical
ABC	ATP-binding cassette
ABCA1/Abca1	ATP-binding cassette transporter A1/ ATP binding cassette subfamily A member 1
ABTS	2,2'-azino-bis(3-ethylbenzthiazoline-6-sulphonic acid)
ACAT-2	Acyl coenzyme A:cholesterol acyltransferase-2
ADMA	Asymmetric dimethylarginine
ALP	Alkaline phosphatase
ALT	Alanine transaminase
AMPK	Adenosine monophosphate-activated protein kinase
Apo	Apolipoprotein
ARE	Antioxidant response element
ARIC	Atherosclerosis Risk in Communities
AST	Aspartate transaminase
BCB	Beta-carotene bleaching
BW	Body weight
CD	Cluster of differentiation
CETP	Cholesteryl ester transfer protein
CHD	Coronary heart disease
CM	Chylomicron
CR	Chylomicron remnant
CRI	Castelli risk index
CRP	C-reactive protein
CTT	Cholesterol treatment trialists
CVD	Cardiovascular disease
CYP7A1/Cyp7a1	Cholesterol 7-α-hydroxylase/ cytochrome P450 7A1
DE	Diosgenin equivalent
DHCR24	3*β*-hydroxysterol ∆24-reductase
DHCR7	7-dehydrocholesterol reductase
DKSM	Defatted kenaf seed meal
DMPO	5,5-dimethyl-*N*-oxide pyroline
DMSO	Dimethyl sulfoxide
DPP	Dimethyallyl pyrophosphate
DPPH	1,1-diphenyl-2-picrylhydrazyl
EA	Ethyl acetate
EDS	Energy Dispersive X-ray Spectrometer
EDTA	Ethylenediaminetetraacetic acid
EGF-A	Epidermal growth factor-like domain A
EL	Endothelial lipase
eNOS	Endothelial NOS
ESR	Electron spin resonance
FDA	Food and Drug Administration
$FeSO_4$	Ferrous sulphate
FH	Familial hypercholesterolemia
FRAP	Ferric reducing antioxidant power
FXR	Farnesoid X receptor
GAE	Gallic acid equivalent
GM-CSF	Granulocyte–macrophage colony stimulating factor

Gpx1	Glutathione peroxidase 1
GSH	Glutathione
Gsr	Glutathione reductase/ glutathione-disulfide reductase
GSSG	Glutathione disulfide
H_2O_2	Hydrogen peroxide
HDL	High-density lipoprotein
HDL-C	HDL cholesterol
HIV	Human immunodeficiency virus
HL	Hepatic lipase
HMG-CoA	3-hydroxy-3-methyl-glutaryl CoA
HMGCR/Hmgcr	HMG-CoA reductase
ICAM-1	Intercellular adhesion molecule-1
IDL	Intermediate-density lipoprotein
IL	Interleukin
IMPROVE-IT	Improved Reduction of Outcomes: Vytorin Efficacy International Trial
IPP	Isopentenyl pyrophosphate
Keap1	Kelch-like ECH-associated protein-1
LC_{50}	Median lethal concentration
LCAT/Lcat	Lecithin-cholesterol acyltransferase
LD_{50}	Median lethal dose
LDL	Low-density lipoprotein
LDL-C	LDL cholesterol
LDLR/Ldlr	LDL receptors
LOX-1	Lectin-like oxLDL receptor
LPL	Lipoprotein lipase
LRC	Lipid research clinics
LRP	LDL receptor-like protein
LXR	Liver X receptor
MCP-1	Monocyte chemoattractant protein-1
M-CSF	Macrophage colony-stimulating factor
$MgCl_2$	Magnesium chloride
MHC	Major-histocompatibilty-complex
MRFIT	Multiple risk factor intervention trial
MTP	Microsomal triglyceride transfer protein
NADPH	Dihydronicotinamide-adenine dinucleotide phosphate
NCEP ATP III	National Cholesterol Education Program, Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III)
NHMS	National Health and Morbidity Survey
NLRP3	NACHT, LRR and PYD domains-containing protein 3
NO	Nitric oxide
NOAEL	No observable adverse effects level
NOS	Nitric oxide synthase
NOX	NADPH oxidases
NPC1L1	Niemann-pick C1-like 1 protein
Nrf2/Nfe2l2	Nuclear factor erythroid 2-related factor 2
$O\cdot_2^-$	Superoxide radical
oxLDL	Oxidized LDL
PCR	Polymerase chain reaction
PCSK9/Pcsk9	Proprotein convertase subtilisin/kexin type 9

PLTP	Phospholipid transfer protein
PP	Farnesyl pyrophosphate
PPAR	Peroxisome proliferator-activated receptor
PSRE	Phenolics-saponins-rich extract
RCT	Reverse cholesterol transport
RE	Rutin equivalent
ROS	Reactive oxygen species
RSD	Relative standard deviation
RT	Reverse transcription
SCAP	SREBP-2 cleavage-activating protein
Sod	Superoxide dismutase
SR-A	Scavenger receptor-A
SR-B1	Scavenger receptor class B type 1
SRE	Sterol response element
SREBP-2	Sterol regulatory element-binding protein-2
TAC	Total antioxidant capacity
TC	Total cholesterol
TEAC	Trolox equivalent antioxidant capacity
Teq.	Trolox equivalent
TFC	Total flavonoid content
TG	Triacylglycerols
TLC	Therapeutic lifestyle changes
TLR	Toll-like receptor
TNF-α	Tumour necrosis factor-alpha
TPC	Total phenolic content
Trolox	6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid
TSC	Total saponin content
TSSC	Total steroidal saponin content
TXA2	Thromboxane A2
VCAM-1	Vascular cell adhesion protein 1
VLDL	Very low-density lipoprotein
WHO	World Health Organization

CHAPTER 1

INTRODUCTION

1.1 Introduction

For the past few decades, cardiovascular diseases (CVDs) persistently remain as the leading cause of global mortality (WHO, 2017). Atherosclerosis, characterized by intimal lipid deposition and abnormal remodelling of the arterial wall in the medium to large arteries (*e.g.* aorta and carotid arteries), underlies the pathogenesis of CVD and contributes to approximately 85% of CVD-related fatalities worldwide (Naghavi et al., 2015). According to the latest report from World Health Organization (WHO), CVD claimed over 17.7 million lives in 2015, accounting for nearly half of the non-communicable diseases deaths and one-third of all deaths globally (WHO, 2017). In Malaysia, ischemic heart disease remains as a primary cause of death for the past 10 years (2005 to 2014), accounting for 13.5% of all deaths in 2014 (Department of Statistics Malaysia, 2016).

CVD is a heavy burden to the economy and health care systems of the country, in terms of direct (*e.g.* hospitalizations, physician visits, rehabilitation services, medications) and indirect costs related to mortality and morbidity (*e.g.* losses of productivity due to premature mortality and short/long term disability). In 2010, the global cost of CVD was estimated at USD 863 billion and the cost is projected to rise by 22% to USD 1,044 billion in year 2030 (Bloom et al., 2011)

Hypercholesterolemia, a pathological condition characterized by undesirably high level of cholesterol (particularly LDL and non-HDL cholesterols) in the blood, is one of the most prominent and modifiable risk factors for atherosclerosis (Steinberg, 2002). Serum total cholesterol level is strongly correlated to the cardiovascular risk; while low-density lipoprotein (LDL) cholesterol is culpably involved in a spectrum of atherosclerotic processes (Ference et al., 2017). Every year, approximately 4.4 million of global death is attributed to hypercholesterolemia (Farzadfar et al., 2011) and the rising trend of hypercholesterolemic prevalence in Malaysia is very worrying. In 2015, the national prevalence of hypercholesterolemia among Malaysian adults is alarmingly high (47.7%), affecting nearly 9.6 million of Malaysians (Institute for Public Health, 2015).

Owing to the undisputed effectiveness in lowering serum LDL cholesterol level, statins are the first-line drugs prescribed in clinical practice for the primary and secondary prevention of CVD (Stone et al., 2014). Although statins are generally well-tolerated, some adverse effects such as statin-associated muscle symptoms (ranging from myalgia to fatal rhabdomyolysis), increased risk of diabetes mellitus, liver damage and cognitive impairment have been reported in some clinical studies (Chaipichit et al., 2015; Evans and Golomb,

2009; Preiss and Sattar, 2011). Furthermore, there are mounting scientific evidences that suggest the presence of a considerable residual risk of CVD in statin-treated patients, even after their therapeutic LDL cholesterol goals are attained (Alagona, 2009).

In the recent years, functional foods and nutraceuticals have been increasingly studied and proposed by the researchers as alternative/ complementary lipid-modifying therapies, particularly for patients with statin-intolerance and resistance (Chen et al., 2008; Chen et al., 2011). Besides, consumption of lipid-modifying/ anti-hypercholesterolemic functional foods and nutraceuticals is one of the feasible approaches for individuals with borderline hypercholesterolemia to improve their pro-atherogenic blood lipid profiles prior to the initiation of pharmacotherapies. Moreover, the lipid-modifying efficacy and safety of some functional foods and nutraceuticals have been well-documented in randomized controlled trials and meta-analyses (Chen et al., 2014a). Green tea, soy protein, red yeast rice, phytosterols and fish oil are some of the good examples of functional foods and nutraceuticals with clinically proven hypocholesterolemic efficacies (Hunter and Hegele, 2017). Due to the complexity of bioactive content (*e.g.* polyphenols, saponins, soluble fibers, fatty acids) and their possible synergistic interactions, some functional foods and nutraceuticals may alleviate the serum lipid abnormalities through the combination of multiple lipid-modifying mechanisms (Chen et al., 2014a; Imam et al., 2016). These mechanisms may include the suppression of hepatic cholesterol biosynthesis, sequestration of bile acids, inhibition of intestinal cholesterol absorption, improvement of circulating cholesterol uptake, enhancement of cholesterol catabolism and so on (Chen et al., 2008).

According to the latest market report, global cardiovascular health market was valued at USD 8.2 billion in 2016 (Euromonitor International, 2017). The increasing consumer health awareness has stimulated the exponential growth of global functional foods market recently. The global functional foods market is promising and progressively growing, with a rising revenue projection of 47.5%, from USD 299.32 billion in 2017 to USD 441.56 billion in 2022 (Statista, 2018). Looking at the upward trend in the use of functional foods/ nutraceuticals in maintenance of cardiometabolic health and prevention of CVD, the development of cardioprotective functional food ingredients with potent anti-hypercholesterolemic, antioxidant and anti-inflammatory properties is crucially needed.

Kenaf (*Hibiscus cannabinus* L.) is an herbaceous, annual/biennial and short-day cordage crop, whose stem and stalk have been commercially used in producing biocomposites, high quality paper, fibre boards and bioplastics. The world production of kenaf and other allied crops was estimated at 232.8 thousand tonnes in year 2014/ 2015, with over 70 % of the global production was contributed by India and China (FAO, 2016). Malaysian government has been continuously promoting the plantation of kenaf as the upcoming national industrial crop in order to replace tobacco plantation (Basri et al., 2014). In Malaysia, the seed yield of kenaf (variety V36) plantation is estimated at 400

kg/ hectare, although some studies from different geographical locations have reported a higher seed yield of over 1000 kg/ hectare (National Kenaf and Tobacco Board, 2010; Webber III et al., 2002). Since seedling for a hectare of kenaf plantation only requires 8 kg of seed (~2% of total seed production), kenaf seeds are considered as an agricultural by-product (Rajashekher et al., 1993; Webber III et al., 2002).

Recent studies show that kenaf seed oil is potentially used as functional edible oil with high antioxidant and anti-cancer properties (Abd Ghafar et al., 2013; Chan and Ismail, 2009; Cheng et al., 2016; Yazan et al., 2011). Since kenaf seed only contains approximately 20% oil (Chan and Ismail, 2009), massive extraction of kenaf seed oil will eventually produce large amounts of secondary by-product, *i.e.* the defatted kenaf seed meal (DKSM). DKSM may still contain considerable amount of non-lipidic nutrients and bioactives (*e.g.* phenolic compounds and saponins), which are potentially used as cardioprotective functional foods/ nutraceuticals. In particular, the cardioprotective properties of phenolic compounds and saponins, involving their anti-hypercholesterolemic, antioxidative and anti-inflammatory effects, have been extensively reported in previous studies (Manach et al., 2005; Singh and Chaudhuri, 2018). At the present, studies on cardioprotective properties of DKSM and its-derived bioactive rich extract are scarce. Thus, further investigations are required to optimally explore the potential health benefits of this underutilized kenaf by-product.

Development of value-added functional food ingredients from DKSM is an innovative, novel, sustainable, environmental friendly and economically viable concept. Optimal utilization of DKSM could significantly add values to the kenaf commodity, minimize the agricultural waste disposal and lower the production cost of functional food ingredients. The developed functional food ingredients are expected to provide a healthier choice to the community in their daily food selection. In the long run, it is hoped that the functional food ingredients developed from DKSM will gradually help in reducing the CVD burden of the country. Moreover, DKSM-based functional food ingredients may generate promising revenue to the nation upon their successful commercialization. With the concept of “Turning Waste to Health and Wealth”, this study is expected to bring positive impacts to the community health, environment and economy of the country.

1.2 Objectives

General objective:

To investigate the cholesterol-lowering properties of defatted kenaf seed meal (DKSM) and its phenolics-saponins-rich extract (PSRE) in a rat model.

Specific objectives:

1. To examine the nutritional quality, phenolic content, antioxidant properties and acute oral toxicity of DKSM as a functional food ingredient.

2. To determine the roles of phenolics and saponins in the antioxidant properties of DKSM via extraction and characterization of PSRE.

3. To evaluate the dietary effects of DKSM and its PSRE on the body weight, hepatosteatosis, serum lipid profile, atherogenic risk indexes and toxicity biomarkers of the hypercholesterolemic rats.

4. To assess the dietary effects of DKSM and its PSRE on the serum total antioxidant capacity as well as oxidative stress and pro-inflammatory biomarkers of the hypercholesterolemic rats.

5. To assess the nutrigenomic effects of DKSM and its PSRE on the transcriptional regulations of cholesterol metabolism and endogenous antioxidant defense in the hypercholesterolemic rat model.

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