



UNIVERSITI PUTRA MALAYSIA

**EFFECTS OF OIL PALM FROND METHANOLIC EXTRACT ON BLOOD
PRESSURE, ANTIOXIDANT STATUS AND SELECTED ORGANS OF
NITRIC OXIDE-DEFICIENT RATS**

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EXTRACT ON BLOOD PRESSURE, ANTIOXIDANT
STATUS AND SELECTED ORGANS OF NITRIC
OXIDE-DEFICIENT RATS**

By

JULIANA BT MD JAFFRI

**This thesis submitted to the School of Graduate Studies, University Putra
Malaysia, in Fulfillment of the Requirements for the Degree of
Doctor of Philosophy**

May 2009



DEDICATIONS

This thesis is dedicated to my late mother, who passed on before I completed this study, and who would have been very proud of my achievements.



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

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Hypertension is a modifiable risk factor for cardiovascular disease (CVD). Diet intervention by increasing the intake of fruits and vegetables proved to be beneficial by reducing blood pressure (BP) and lowering the risk of CVD. Apart from micronutrients, the phytochemical content of fruits and vegetables has been associated with the BP lowering effect. Hypertension is commonly associated with a reduced vascular nitric oxide (NO) due to excessive degradation by reactive oxygen species (ROS). In addition, NO is also important in maintaining organ functions and perfusion. In this study normal and NO deficient rats were used to evaluate the BP lowering effect and antioxidative property of oil palm frond methanolic extract (OPFME). The protective effect of OPFME in the liver, heart, kidney and brain of these rats were assessed and any toxicity effect was also investigated. Two major groups of rats (normal and NO deficient groups) were further divided into three sub-groups; the first subgroup received the vehicle used to dilute OPFME; the

second subgroup received OPFME and the third subgroup received captopril. NO deficiency was induced by administration of N- ω -nitro-L-arginine methyl ester (L-NAME). Erythrocyte/organ superoxide dismutase (SOD), catalase and glutathione peroxidase (GPx) activities, and plasma/organ malondialdehyde (MDA) concentration were measured. Livers, hearts, kidneys and brains were removed at the end of the study. Histological appearances of these organs were examined. Kidneys were functionally evaluated by measurement of plasma creatinine and urea concentrations, whereas liver function was tested by measuring plasma alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP). OPFME significantly attenuated BP increases in NO deficient rats comparable to captopril, and temporarily improved antioxidant status. In the liver OPFME partially protected hepatocytes from extensive injury due to NO deficiency. OPFME also partially prevented coronary arterioles from thickening, but failed to inhibit structural changes in the left ventricle. The glomeruli of OPFME treated NO deficient rats were not improved. Slight renal tubular dilation observed in normal rats treated with OPFME is a matter of concern and should be further investigated. OPFME showed remarkable hippocampal neuroprotection and this correlated well with its antioxidative property in the brain. There was no neurotoxic effect of OPFME observed. On the contrary, neurogenesis was displayed as an increase in the number of viable granule cells of the dentate gyrus (DG) of normal rats treated with OPFME. In conclusion, OPFME was effective in suppressing BP increment during NO deficiency. The extract was also partially hepatoprotective and significantly neuroprotective. However, OPFME may induce nephrotoxicity and should be investigated further for clarification.

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

**KESAN EKSTRAK METHANOL DAUN KELAPA SAWIT TERHADAP TEKANAN DARAH,
TAHAP ANTIOKSIDAN DAN ORGAN TERPILIH PADA TIKUS KEKURANGAN NITRIK
OKSIDA**

Oleh

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Hipertensi adalah factor risiko penyakit kardiovaskular yang boleh diatasi. Pengubahsuaian cara pemakanan dengan melebihkan buah-buahan dan sayur-sayuran telah terbukti dapat mengurangkan tekanan darah serta mengurangkan risiko penyakit kardiovaskular. Selain dari zat-zat makanan asas, kandungan polifenol buah-buahan dan sayur-sayuran juga dikaitkan dengan penurunan tekanan darah. Hipertensi adalah penyakit yang sering dikaitkan dengan penurunan kandungan nitrik oksida vaskular akibat tindakbalas radikal oksigen yang tidak terkawal. Nitrik oksida juga adalah penting untuk fungsi dan pengaliran darah ke organ-organ badan. Kajian ini dijalankan untuk menilai kesan ekstrak daun kelapa sawit terhadap penurunan tekanan darah dan tahap antioksidan badan. Kesan-kesan terhadap hati, ginjal, jantung dan otak juga dikaji untuk menentukan tahap perlindungan dari kegagalan yang berpunca dari kekurangan nitrik oksida. Selain daripada itu pemerhatian terhadap kesan-kesan toksik ekstrak daun kelapa sawit

juga dijalankan. Tikus digunakan untuk kajian ini, dan telah dibahagikan kepada dua kumpulan utama iaitu normal dan kekurangan nitrik oksida. Setiap kumpulan dibahagikan kepada tiga kumpulan kecil mengikut rawatan yang diberikan. Kumpulan pertama menerima pelarut yang digunakan untuk melarutkan ekstrak, kumpulan kedua menerima ekstrak dan kumpulan ketiga menerima captopril. Kesan kekurangan nitrik oksida dihasilkan daripada pemberian N- ω -nitro-L-arginine methyl ester (L-NAME). Tahap aktiviti superoxide dismutase (SOD), catalase dan glutathione peroxidase (GPx) dalam sel darah merah/organ serta kandungan malondialdehyde plasma/organ dikaji. Organ-organ yang dipilih untuk dikaji adalah hati, ginjal, jantung dan otak. Kajian histologi dilakukan ke atas organ-organ tersebut. Tahap creatinine plasma dan urea dilakukan untuk menentukan fungsi ginjal, manakala kandungan alanine aminotransferase (ALT), aspartate aminotransferase (AST), dan alkaline phosphatase (ALP) dilakukan untuk menentukan fungsi hati. Ekstrak daun kelapa sawit didapati berkesan mengekalkan tekanan darah normal. Tahap antioksidan juga bertambah baik dengan pengambilan ekstrak walaupun tidak kekal hingga ke akhir tempoh kajian. Ekstrak tersebut juga didapati meredakan kerosakan sel hati yang teruk akibat kekurangan nitrik oksida, serta mengurangkan (tidak ketara) penebalan salur darah koronari tetapi tidak berkesan merencat perubahan struktur pada ventrikel kiri jantung. Tiada kesan perlindungan diperhatikan di glomerulus. Ekstrak didapati menyebabkan sedikit pembengkakan pada tiub ginjal, dan ianya perlu dikaji dengan lebih lanjut. Kesan ekstrak pada sel-sel otak di hippocampus adalah sangat baik di mana ianya mungkin disebabkan oleh peningkatan tahap antioksidan otak. Tiada kesan sampingan berlaku di organ ini akibat rawatan ekstrak, malah di bahagian dentate

gyrus sel-sel neuron didapati bertambah bilangannya. Kesimpulannya, ekstrak daun kelapa sawit berkesan mengawal peningkatan tekanan darah semasa di dalam keadaan kekurangan nitrik oksida. Ekstrak juga mengurangkan kegagalan hati (tidak ketara), serta dapat melindungi dari kerosakan sel-sel otak. Walau bagaimana pun ekstrak mungkin boleh menyebabkan kesan toksik di ginjal. Oleh itu, kajian lanjut perlu dijalankan untuk menjelaskan masalah ini.



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TABLE OF CONTENTS

		Page
ABSTRACT		iii
ABSTRAK		v
ACKNOWLEDGEMENT		viii
APPROVAL		NA
DECLARATION		ix
LIST OF TABLES		xiv
LIST OF FIGURES		xvi
LIST OF ABBREVIATIONS		xx
CHAPTER		
1	INTRODUCTION	1
2	LITERATURE REVIEW	
	2.1 The Oil Palm	4
	2.2 The Values of Oil Palm Fronds	5
	2.3 Hypertension and Nutrition	7
	2.4 The Antioxidant Phytochemicals of Oil Palm Fronds	
	2.4.1 Polyphenols	9
	2.4.2 Alpha-Tocopherol	15
	2.4.3 Carotenoids	20
	2.5 Nitric Oxide: Synthesis and Role	23
	2.6 Source of Reactive Oxygen Species	26
	2.7 Antioxidant Defense System	
	2.7.1 Endogenous Enzymes	28
	2.7.2 Endogenous Non-enzymatic Antioxidants	30
	2.8 Lipid Peroxidation Biomarkers	34
	2.8.1 Malondialdehyde	36
	2.8.2 Isoprostanes	37
	2.8.3 Four-Hydroxynonenal	38
	2.9 Vascular ROS and Impaired NO Level	40
	2.10 The Renin-Angiotensin System and Oxidative Stress	41
	2.11 The Mechanism of NOS Inhibition	42
	2.12 The Role of RAS in NO Inhibition	44
	2.13 Vascular Protective Effect of Antioxidant Phytochemicals	46
	2.14 NO Dependant Vasodilation	
	2.14.1 Animal Studies	48
	2.14.2 Human Studies	52
	2.15 Endothelium-derived Hyperpolarizing Factor	54
	2.16 Endothelium-independent Vasodilation	56
	2.17 Major Organ Protective Effects of the Polyphenols, Tocopherols and Carotenoids	
	2.17.1 Effects on the Liver	58
	2.17.2 Effects on the Kidney	63
	2.17.3 Effects on the Brain	66

2.17.4	Effects on the Heart and Arteries	70
2.18	Clinical Biochemistry: Liver Function Tests	
2.18.1	Markers of Cytolysis: The Aminotransferases	73
2.18.2	Markers of Cholestasis: Alkaline Phosphatase	74
2.19	Clinical Biochemistry: Renal Function Tests	
2.19.1	Serum Creatinine	76
2.19.2	Blood Urea Nitrogen	77
3	EFFECTS OF OIL PALM FROND METHANOLIC EXTRACT ON BLOOD PRESSURE AND ANTIOXIDANT STATUS IN NITRIC OXIDE DEFICIENCY	
3.1	INTRODUCTION	78
3.2	MATERIALS AND METHODS	
3.2.1	Chemical	80
3.2.2	Plant Material and Extract Preparation	80
3.2.3	Determination of Total Phenolic Content	81
3.2.4	Animals	82
3.2.5	Blood Sampling	86
3.2.6	Determination of BP	87
3.2.7	Serum Nitric Oxide measurement	87
3.2.8	Determination of Erythrocyte Antioxidant Activities	88
3.2.9	Determination of Plasma MDA	90
3.2.10	Statistical Analysis	91
3.3	RESULT	
3.3.1	Total Phenolic Content of OPFME	92
3.3.2	Weight Gain	92
3.3.3	Feed Intake	93
3.3.4	Blood Pressure	96
3.3.5	Serum Nitric Oxide Concentration	99
3.3.6	Plasma MDA Concentration	101
3.3.7	Antioxidant Enzyme Activities	101
3.4	DISCUSSION	107
3.5	CONCLUSION	111
4	EVALUATION OF OIL PALM FROND METHANOLIC EXTRACT AS A HEPATOPROTECTIVE AGENT IN NITRIC OXIDE DEFICIENCY	
4.1	INTRODUCTION	112
4.2	MATERIALS AND METHODS	
4.2.1	Chemical	113
4.2.2	Plant Material and Extract Preparation	113
4.2.3	Animals	114
4.2.4	Blood and Liver Sampling	114
4.2.5	Biochemical Analyses of Plasma	115
4.2.6	Histology Study	115
4.2.7	Determination of Liver Antioxidant Enzyme Activities	116

4.2.8	Determination of Liver MDA Contents	116
4.2.9	Statistical Analysis	117
4.3	RESULT	
4.3.1	Plasma Biochemistry	118
4.3.2	Percentage Abnormal Cells	123
4.3.3	Histopathology	123
4.3.4	Liver Antioxidant Status and HSI	126
4.4	DISCUSSION	128
4.5	CONCLUSION	133
5	EVALUATION OF OIL PALM FROND METHANOLIC EXTRACT AS A PROTECTIVE AGENT AGAINST KIDNEY AND HEART DAMAGES IN NITRIC OXIDE DEFICIENCY	
5.1	INTRODUCTION	134
5.2	MATERIALS AND METHODS	
5.2.1	Chemical	135
5.2.2	Plant material and extract preparation	135
5.2.3	Animals	135
5.2.4	Blood and Organ Sampling	136
5.2.5	Biochemical Analyses of Plasma	137
5.2.6	Histology Study	137
5.2.7	Determination of Heart and Kidney Antioxidant Enzyme Activities	138
5.2.8	Determination of Heart and Kidney MDA Contents	138
5.2.9	Statistical Analysis	138
5.3	RESULT	
5.3.1	Water Intake	139
5.3.2	Kidney and Heart Abnormal Cells	139
5.3.3	BUN	143
5.3.4	Creatinine	144
5.3.5	Antioxidant Status	145
5.3.6	Somatic Indices	148
5.3.7	Histopathology	150
5.4	DISCUSSION	159
5.5	CONCLUSION	164
6	EVALUATION OF OIL PALM FROND METHANOLIC EXTRACT AS A NEUROPROTECTIVE AGENT IN NITRIC OXIDE DEFICIENCY	
6.1	INTRODUCTION	165
6.2	MATERIALS AND METHODS	
6.2.1	Chemical	167
6.2.2	Plant Material and Extract Preparation	167
6.2.3	Animals	168
6.2.4	Brain Sampling	168
6.2.5	Histology Study	168
6.2.6	Determination of Brain Antioxidant Enzyme	169

	Activities	
6.2.7	Determination of Brain MDA Contents	169
6.2.8	Statistical Analysis	169
6.3	RESULTS	
6.3.1	Viable Neuron Percentage	170
6.3.2	Brain Antioxidant Status	173
6.3.3	Histopathology	176
6.4	DISCUSSION	180
6.5	CONCLUSION	186
7	SUMMARY, CONCLUSION AND RECOMMENDATIONS FOR FUTURE RESEARCH	187
	REFERENCES	191
	BIODATA OF STUDENT	239

LIST OF TABLES

Table		Page
2.1	Estimated daily average of the polyphenol, carotenoid, and phytosterol content (mg/1,000 kcal) of the control and DASH diet menus used in the DASH study.	8
2.2	The activity of plant / plant-derived polyphenols on isolated vessels	49-50
3.1	Crude nutritional values of the standard laboratory chow fed to the experimental rats.	82
3.1	Animal weight gain during the experimental study	92
3.3 ^a	Weekly feed intake of experimental rats during the study (week 0 to 6)	94
3.3 ^b	Weekly feed intake of experimental rats during the study (week 7 to 12)	95
3.4	Serum nitric oxide values (ppm) of experimental rats at different point in time of the study	100
3.5	Plasma MDA concentration ($\mu\text{mol/L}$) of experimental rats at different point in time of the study	102
3.6	Erythrocyte SOD activities (value $\times 10^{-2}$ unit/ml) of experimental rats at different point in time of the study	103
3.7	Erythrocyte catalase activities (value $\times 10^{-2}$ k/ml) of experimental rats at different point in time of the study	105
3.8	Erythrocyte GPx activities (unit/ml) of experimental rats at different point in time of the study	106
4.1	Activities of liver SOD, catalase and GPx , MDA level and HSI in the experimental rats	127
5.1	Animal water intake (ml) during the experimental study	140
5.2	Plasma BUN (mmol/L) of experimental rats	143
5.3	Plasma creatinine ($\mu\text{mol/L}$) of experimental rats	144
5.4	Renal SOD, catalase and GPx activities, and MDA level of experimental rats	146

5.5	Activities of heart SOD, catalase and GPx, and MDA level of experimental rats	147
5.6	Renal and cardio-somatic indexes of experimental rats	149
6.1	Activities of brain SOD, catalase and GPx, and MDA level of experimental rats	175



LIST OF FIGURES

Figure		Page
2.1	Oil palm tree typically grown in Malaysia (left). Note the abundance of green fronds, the uppermost being the youngest. Picture on the right is a frond from a young oil palm tree.	5
2.2	Structures of some common simple phenolic acids	10
2.3	The six main classes of flavonoids	10
2.4	Functional groups of quercetin known for its high antioxidant capacity	12
2.5	Quercetin binding sites for trace metals	13
2.6	Stereoisomers of tocopherols. The tocotrienols differ from the analogous tocopherols by the presence of three double bonds in the hydrophobic side chain.	15
2.7	The chain breaking antioxidant activities of α -tocopherol	18
2.8	The structures of β -carotene (A) and lycopene (B) with the functional polyene chain.	21
2.9	The vasodilating mechanism of vascular NO.	25
2.10	Structure homology of the hepatoprotective polyphenols	62
3.1	Crude nutritional values of the standard laboratory chow fed to the experimental rats.	82
3.2	Experimental design of the study. Each major group was subdivided into three groups according to the treatment given. NO deficient rats were given L-NAME in the drinking water and the different treatments simultaneously. The group in the filled textbox represents the control of this study.	84
3.3	SBP of the three NO deficient rat groups compared to control	97
3.4	SBP of the three normal rat groups. The control group is the same as in Figure 3.1.	98
4.1	Plasma ALT of experimental rats at baseline and at the end of the study	119

4.2	Plasma AST of experimental rats at baseline and at the end of the study	120
4.3	Plasma ALP of experimental rats at baseline and at the end of the study	122
4.4	Percentage of abnormal hepatocytes observed in the livers of experimental rats	124
4.5	Photomicrographs of the livers of experimental rats at the end of the study. A: control; B: OPFME; C: captopril; D: L-NAME; E: L-NAME+OPFME; F: L-NAME+captopril. While the microscopic appearance of livers of rats from the A, B, C and E groups were within normal limits, those of the D and F groups exhibited degenerative and necrotic changes. Inflammatory cells (yellow arrow) and portal tract congestion (X) were also present in L-NAME liver. (H&E, X400).	125
5.1	Percentage of abnormal glomeruli observed in experimental rats	141
5.2	Percentage of myocardial fibrosis observed in experimental rats	142
5.3	Photomicrographs of kidney sections of normal rats at the end of the study showing glomeruli of normal appearance in different groups. A and B: control; C and D: OPFME; E and F: captopril. (H&E; A, C, E – X100; B, D, F – X400).	151
5.4	Photomicrographs of kidney sections of NO deficient rats. A and B: L-NAME; C and D: L-NAME+OPFME; E and F: L-NAME+captopril. Glomerular injury was prominent in all groups and a substantial arterial wall thickening (white arrow) was present in B and F. In C and E glomerular capillary adhesion to Bowman’s capsule indicates glomerular injury whilst in B inflammatory cells were present at the capillary tuft and surrounding the glomerulus (black arrow). Note that there are also normal glomerulus scattered throughout the kidneys (N). (H&E; A, C, E – X100; B, D, F – X400).	152
5.5	Photomicrographs of renal tubular sections of the experimental rats at the end of the study. A: control; B: OPFME; C: captopril; D: L-NAME; E: L-NAME+OPFME; F: L-NAME+captopril. In D, E and F tubular dilation occurred in patches among normal structures. C showed extensive tubular damage with prominent vacuolation. There was an increase in peritubular space (arrows) in E whilst in B, the tubules were slightly swollen. (H&E, X400).	153
5.6	Photomicrographs of the left ventricle myocardium of	155

experimental rats in longitudinal section. A: control; B: OPFME; C: captopril; D: L-NAME; E: L-NAME+OPFME; F: L-NAME+captopril. All NO deficient rats showed extensive myocardial fibrosis (black arrow). The muscle fibres of group D and E were also thicker indicating hypertrophy, while those of group B, C and F were similar to A. (H&E, X100).

5.7	Myocardial fibre thickness of experimental rats	156
5.8	Photomicrographs of coronary arterioles of experimental rats at the end of the study. A: control; B: OPFME; C: captopril; D: L-NAME; E: L-NAME+OPFME; F: L-NAME+captopril. There was an increase in arterial wall thickness with perivascular fibrosis in D, whilst in E wall thickness was partially reduced. A, B and C showed normal arteries. Myocardial fibrosis was also prominent in F. (H&E, X400).	157
5.9	Coronary arteriole wall to lumen ratio of experimental rats	158
6.1	Hippocampal CA1 pyramidal cell viability in experimental rats	171
6.2	Hippocampal CA3 pyramidal cell viability in experimental rats	172
6.3	Hippocampal DG granule cell viability in experimental rats	174
6.4	Photomicrographs of the hippocampus CA1 subfield of experimental rats. A: control; B: OPFME; C: captopril; D: L-NAME; E: L-NAME+OPFME; F: L-NAME+captopril. Unlike the other experimental groups, most of the nerve cells in D appeared dark and shrunken with the loss of nucleus, indicating neurodegeneration. In E and F, neurodegeneration was attenuated with the presence of dark neurons interspersed among the normal nerve cells. (H&E, X400).	177
6.5	Photomicrographs of the hippocampus CA3 subfield of experimental rats. A: control; B: OPFME; C: captopril; D: L-NAME; E: L-NAME+OPFME; F: L-NAME+captopril. Dark and shrunken neurons are scattered occasionally in A as normal aging occurred. The same pattern was observed in B and C. In D neuron loss was prominent and the number of normal neurons in the row of nerve cells was decreased. OPFME and captopril treatments in NO deficiency (E and F respectively) effectively increased neuron survival from the low NO state. (H&E, X400).	178
6.6	Photomicrographs of the hippocampus DG subfield of experimental rats. A: control; B: OPFME; C: captopril; D: L-NAME; E: L-NAME+OPFME; F: L-NAME+captopril. The amount of	179

shrunken and dark neurons in the row of nerve cells in D and F are greater than the rest of the groups. In E, more neurons were protected from L-NAME induced damages. The number of neurons in B was markedly increased when compared to A, implying that OPFME enhanced neurogenesis in the DG. In C, there was also a moderate increase in viable neurons. (H&E, X400).



LIST OF ABBREVIATIONS

$\cdot\text{O}_2^-$	Superoxide
$\cdot\text{OH}^-$	Hydroxyl radical
ACE	Angiotensin converting enzyme
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
ARB	Angiotensin II receptor blocker
AST	Aspartate aminotransferase
AT ₁	Angiotensin II Type 1
BHT	Butylated hydroxytoluene
BP	Blood pressure
BSA	Bovine serum albumin
BUN	Blood urea nitrogen
CA	Cornu Ammonis
cAMP	Cyclic adenosine monophosphate
cGMP	Cyclic guanosine monophosphate
CNS	Central nervous system
Cu/ZnSOD	Copper and zinc superoxide dismutase
CVD	Cardiovascular disease
DASH	Dietary approach to stop hypertension
DG	Dentate gyrus
DTNB	dithio-bis(2-nitrobenzoic acid)

EC-SOD	Extracellular superoxide dismutase
EDHF	Endothelium derived hyperpolarizing factor
EDTA	Ethylene diamine triacetic acid
eNOS	Endothelial nitric oxide synthase
GAE	Gallic acid equivalent
GPx	Glutathione peroxidase
GSH	Reduced glutathione
GTP	Guanosine triphosphate
H&E	Hematoxylin-eosin
HSI	Hepatosomatic index
iNOS	Inducible nitric oxide synthase
L-NAME	N- ω -nitro-L-arginine methyl ester
LSEC	Liver sinusoidal endothelial cell
LVH	Left ventricular hypertrophy
MDA	Malondialdehyde
MnSOD	Manganese superoxide dismutase
NADH	Nicotinamide adenine dinucleotide, reduced form
NADPH	Nicotinamide adenine dinucleotide phosphate, reduced form
NF- κ B	Nuclear factor kappa B
NMDA	N-methyl-D-aspartate
nNOS	Neuronal nitric oxide synthase
NOS	Nitric oxide synthase
OPFME	Oil palm frond methanolic extract

PGE ₂	Prostaglandin E ₂
PUFA	Polyunsaturated fatty acid
RAS	Renin angiotensin system
ROS	Reactive oxygen species
RWP	Red wine polyphenols
SDS	Sodium dodecyl sulfate
SOD	Superoxide dismutase
TBA	Thiobarbituric acid
TEP	1,1,3,3-tetraethoxypropane
TPC	Total phenolic content
UPM	Universiti Putra Malaysia
VSM	Vascular smooth muscle
WKY	Wistar Kyoto

CHAPTER 1

INTRODUCTION

Hypertension is a lifestyle related disease which can be devastating if complicated. It is a common risk factor for CVD (Schnall et al, 2000; Grundy et al, 1999), affecting millions of people throughout the world and in 2006 about 43% of the adult Malaysian population (30 years and above) have diastolic blood pressure of 90 mmHg or greater, a relative increase of 30% from that of 10 years earlier (Ministry of Health, 2008).

There is still much uncertainty about the pathophysiology of hypertension. Decreased level of NO, a very important mediator of vasorelaxation, is a well known factor for increased blood pressure (Forte et al, 1997). This condition is also associated with obesity/insulin resistance, whereby obese/insulin-resistant subjects are characterized by endothelial dysfunction and endothelial resistance to insulin's effect on enhancement of endothelium-dependent vasodilation (Steinberg et al, 1996). The low NO level could contribute to the development of hypertension. Epidemiological studies indicate that two major determinants of human morbidity and mortality, arterial hypertension and insulin resistance, are related, suggesting the possibility of a common underlying mechanism (Duplain et al, 2001; Modan et al, 1985; Lucas et al, 1985).

CVD development is a multi-factorial process in which endothelial dysfunction, inflammatory response, dyslipidemia, and activated platelets all play significant role in the process (Hansson, 2005; Libby and Simon, 2001). The seriousness of the Malaysian situation has prompted The Ministry of Health to launch a number of campaigns in an effort to prevent CVD from becoming widespread. As the rising number of individuals with hypertension are identified and treated, the incremental burden on the Malaysian government healthcare system could be staggering.

A nutritional approach to this problem would be especially appealing, because it could minimize both the healthcare workload and the cost of therapy. In addition, nutritional approach rarely results in unwanted side effects, which is very common with most pharmacological therapy. Based on the Dietary Approach to Stop Hypertension (DASH) diet (Most et al, 2004), the intake of plant foods high in phytochemicals is associated with lowering of BP. An alternative way of increasing phytochemical intake is through supplementation with plant based nutraceuticals, in a convenient capsule/tablet form that is compact and easy to take. Individuals with strong family history of obesity and metabolic syndrome may benefit from this approach, as the problem is usually dealt with at an early stage, whereby it is still uncomplicated and reversal of the condition is possible. Oil palm frond extract may be a good candidate for a nutraceutical in this category, which may help reduce the risk of developing hypertension in individuals with low endothelial NO.

The majority of nutraceuticals in Malaysia is imported from countries such as USA and Australia, utilizing plants from the temperate climate. This is one of the reasons