UNIVERSITI PUTRA MALAYSIA

PHYTOCOMPONENTS, SAFETY, ANTIOXIDANT, ANTI-INFLAMMATORY, HYPOCHOLESTEROLEMIC AND ANTI-ATHEROSCLEROTIC PROPERTIES OF BASELLA ALBA L. LEAF EXTRACT

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FBSB 2015 23

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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

June 2015

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

PHYTOCOMPONENTS, SAFETY, ANTIOXIDANT, ANTI-INFLAMMATORY, HYPOCHOLESTEROLEMIC AND ANTI-ATHEROSCLEROTIC PROPERTIES OF *BASELLA ALBA* L. LEAF EXTRACT

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June 2015

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Hypercholesterolemia is the major risk factor that leads to atherosclerosis, which is the primary cause of death in world population. Nowadays, alternative treatment using medicinal plants gained much attention since the treatment using synthetic drug, statins, lead to adverse health effects, especially liver and muscle toxicity. Thus, the focus of this study was on *Basella alba* (*B. alba*) leaf extract; its phytocomponents, toxicity, antioxidant, anti-inflammatory, hypocholesterolemic and anti-atherosclerotic properties.

In this study, 25 medicinal plants extracts were screened for anti HMG-CoA reductase activity. *B. alba* leaf extract showed the highest inhibitory effect, about 74%. Therefore, *B. alba* was examined in order to investigate its phytochemical components. Gas Chromatography Mass Spectrometry (GC-MS/MS) analysis detected 25 compounds while Reverse Phase-High Performance Liquid Chromatography (RP-HPLC) revealed the presence of naringin, apigenin, luteolin, ascorbic acid and α-tocopherol. The major compounds of *B. alba* have been reported to possess antihypercholesterolemic effects and further investigation was conducted on *in vivo* model.

The toxicity evaluation of *B. alba* leaf extract was determined using cytoxicity test against Vero and WRL-68 cell lines, acute and subchronic toxicity test in rats. SRB assay revealed non cytotoxic effect of *B. alba* with IC_{50} value of more than 625 µg/ml. The hematological and biochemical analyses showed no significant elevation in the parameters of *B. alba* extract treated rats compared to the control group. Histopathological examination revealed no harmful effects noted in liver and kidney. Cytotoxicity and acute toxicity studies confirmed that *B. alba* extract is non toxic and can be utilized as alternative therapeutic agent.

The present study also seeks to investigate antioxidant, anti-inflammatory, proximate and mineral composition analyses of *B. alba* leaf extract, focusing on therapeutic potential relating to hypercholesterolemia. *B. alba* extract exhibits high antioxidant activity in inhibiting radicals like hydroperoxides, 2,2-diphenyl-1-picrylhydrazyl (DPPH), nitric oxide (NO) and ferric ions. Anti-inhibitory activity of *B. alba* extract on hyaluronidase, xanthine oxidase and lipoxygenase enyzmes demonstrated a desirable anti-inflammatory activities.

Twenty New Zealand white rabbits were divided into 5 groups and fed with normal diet (G1), 2% high cholesterol diet (HCD) (G2), 2% HCD + 10 mg/kg simvastatin (G3), 2% HCD + 100 mg/kg *B. alba* extract (G4) and 2% HCD + 200 mg/kg *B. alba* extract (G5), respectively. The treatment with *B. alba* extract significantly lowered the levels of total cholesterol (TC), low density lipoptotein (LDL) and triglyceride (TG). The significant increase in high density lipoprotein (HDL) and antioxidant enzymes; superoxide dismutase (SOD) and glutathione peroxidase (GPx) levels observed in treatment with *B. alba* extract (G4 and G5) compared to the treatment with simvastatin (G3). The elevated levels of liver enzymes; alanine aminotransferase (ALT) and aspartate aminotransferase (AST), and muscle enzyme; creatine kinase (CK) were noted in G2 and G3 indicate liver and muscle injuries. Treatment with simvastatin (G3) and *B. alba* extract (G4 and G5) significantly suppressed the aortic plaque formation. This is the first *in vivo* study on *B. alba* that suggests its potential as an alternative therapeutic agent for hypercholesterolemia and atherosclerosis.

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

SIFAT-SIFAT FITOKOMPONEN, KESELAMATAN, ANTIOKSIDAN, ANTIKERADANGAN, HIPOKOLESTEROLEMIK DAN ANTI ATEROSKLEROSIS PADA EKSTRAK DAUN *BASELLA ALBA* L.

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Hiperkolesterolemia merupakan faktor risiko utama yang boleh mengakibatkan aterosklerosis, iaitu punca utama kematian penduduk dunia. Kini, rawatan alternatif yang menggunakan tumbuhan ubatan semakin mendapat perhatian kerana rawatan yang menggunakan dadah sintetik iaitu statin boleh menyebabkan kesan kesihatan yang buruk, terutamanya ketoksikan hati dan otot. Oleh itu, fokus kajian ini adalah terhadap ekstrak daun *Basella alba* (*B. alba*); fitokomponen tersebut serta sifat-sifat ketoksikan, bahan antioksida, antiradang, hipokolesterolemik dan antiaterosklerosis oleh tumbuhan tersebut.

Dalam kajian ini, 25 ekstrak tumbuhan ubatan telah disaring untuk mengkaji aktiviti anti-*HMG-CoA* reduktase. Ekstrak daun *B. alba* menunjukkan kesan rencatan tertinggi, iaitu sebanyak 74%. Oleh itu, *B. alba* telah dikaji untuk menyelidik komponen-komponen fitokimianya. Analisis Kromatografi Gas-Spektrometri Jisim (*Gas Chromatography-Mass Spectrometry*, GC-MS/MS) mengesan 25 sebatian, manakala Kromatografi Cecair Prestasi Tinggi Fasa Berbalik (*Reverse Phase-High Performance Liquid Chromatography*, RP-HPLC) mendedahkan kehadiran naringin, apigenin, luteolin, asid askorbik, dan α-tokoferol. Sebatian-sebatian utama dalam *B. alba* didapati mempunyai kesan antihiperkolesterolemik dan siasatan lanjut telah dijalankan terhadap model *in vivo*. Penilaian ketoksikan ekstrak daun *B. alba* dilaksanakan dengan melakukan ujian kesitotoksikan terhadap titisan sel Vero dan WRL-68, ujian ketoksikan akut dan subkronik pada tikus. Asai sulforhodamin (SRB) menunjukkan kesan bukan sitotoksik *B. alba* dengan nilai IC_{50} yang lebih daripada 625 µg/mL. Analisis hematologi dan biokimia tidak menunjukkan sebarang peningkatan ketara pada parameter-parameter kumpulan tikus yang dirawat dengan ekstrak *B. alba* berbanding dengan kumpulan kawalan. Pemeriksaan histopatologi menunjukkan ketiadaan sebarang kesan berbahaya pada hati dan buah pinggang. Kajian kesitotoksikan dan ketoksikan akut mengesahkan bahawa ekstrak *B. alba* adalah tidak toksik dan boleh digunakan sebagai agen terapeutik alternatif.

Kajian ini juga bertujuan untuk menyiasat analisis bahan antioksida, antiradang, serta komposisi proksimat dan mineral pada ekstrak daun *B. alba* dengan menumpukan kepada potensi terapeutik yang berkaitan dengan hiperkolesterolemia. Ekstrak *B. alba* mempamerkan aktiviti antioksida yang tinggi bagi merencat bahan radikal seperti

hidroperoksida, 2,2-difenil-1-pikrilhidrazil (*2,2-diphenyl-1-picrylhydrazyl*, DPPH), nitrik oksida (*nitric oxide*, NO), dan ion ferik. Aktiviti antiradang oleh ekstrak *B. alba* terhadap hialuronidase, oksidase xantina, dan enzim lipoksigenase mempamerkan aktiviti antiradang yang diingini.

Dua puluh ekor arnab putih New Zealand telah dibahagikan kepada 5 buah kumpulan, dan masing-masing diberikan makan dengan diet yang normal (G1), 2% diet berkolesterol tinggi (HCD) (G2), 2% HCD + 10 mg/kg simvastatin (G3), 2% HCD + 100 mg/kg ekstrak *B. alba* (G4), dan 2% HCD + 200 mg/kg ekstrak *B. alba* (G5). Rawatan dengan ekstrak *B. alba* menurunkan paras jumlah kolesterol (*total cholesterol*, TC), lipoprotein ketumpatan rendah (*low density lipoprotein*, LDL) dan trigliserida (*triglyceride*, TG). Peningkatan ketara pada lipoprotein ketumpatan tinggi (*high density lipoprotein*, HDL), dan enzim antioksida; tahap superoksida dismutase (*superoxide dismutase*, SOD) dan glutation peroksidase (*glutathione peroxidase*, GPx), diperhatikan dalam rawatan yang mengandungi ekstrak *B. alba* (G4 dan G5) berbanding dengan rawatan yang mengandungi simvastatin (G3). Peningkatan tahap enzim hati; alanina aminotransferase (*alanine aminotransferase*, ALT) dan aspartat aminotransferase (*aspartate aminotransferase*, AST), serta enzim otot; kreatina kinase (*creatine kinase*, CK) yang diperhatikan dalam G2 dan G3 menandakan kecederaan hati dan otot. Rawatan dengan simvastatin (G3) dan ekstrak *B. alba* (G4 dan G5) menyekat pembentukan plak aorta dengan amat ketara. Kajian *in vivo B. alba* ini merupakan kajian pertama yang mencadangkan potensinya sebagai agen terapeutik alternatif bagi merawat hiperkolesterolemia dan aterosklerosis.

ACKNOWLEDGEMENTS

This thesis is a conclusion of my PhD project which started on 26th September 2011 at Lab 204, Department of Biochemistry, Faculty of Biotechnology and Biomolecular Sciences, UPM. I am very glad and thankful to Baba, for His blessings for me to finish up this thesis successfully. I would like to express my gratitude to my beloved family, Mr. Gunasekaran, Mrs Ramani, Mr Samalan and Tommy for allowing me to further my studies until this stage, for their encouragements and continuous support that keep me going on my journey.

I will forever be very thankful to my supervisor, Associate Professor Dr. Mohd. Yunus Abdul Shukor, for his trust, invaluable guidance, continuous support, advices and constructive suggestions that have helped me throughout my studies. Besides, I am also grateful to my supervisory committee members: Dr Siti Aqlima Ahmad, Dr Azmi Shaharuddin and Assoc Prof Dr Azrina Azlan for their insightful comments and guidance.

I owe my deepest appreciation to Shamala Salvamani for being there during my toughest time in life and throughout the PhD studies. This PhD definitely cannot be achieved without you. Thanks for the good sharing and undivided support.

Not to forget my well wishers, Parveen Devi and Madhava ji for their prayers, encouragement and constant support. I also would like to express my gratitude to all the good souls (rabbits and rats) that have been sacrificed during this study.

During my studies, I have enjoyed the association with many colleagues (MARDI, FRIM, UKM, UM and natural therapy centers) and I wish to extend my warmest thanks to all of them. Definitely, the sharing of the ideas and suggestions has helped me a lot for the completion of this study.

Finally, I would like to thank those who have said "No" to me in life. It is because of all of you, I am in this stage today. God Bless all.

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

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LIST OF ABBREVIATIONS

Ab_b	absorbance of blank
Ab_c	absorbance of control
Ab_s	absorbance of sample
ACE	angiotensin converting enzyme
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANOVA	analysis of variance
AOAC	Association of Official Analytical Chemists
AST	aspartate aminotransferase
ATP	adenine trinucleotide phosphates
B. alba	*Basella alba*
°C	degree Celcius
°C /min	degree Celcius per minute
CETP	cholesterol ester transfer protein
CK	creatine kinase
cm	centimetre
CO_2	carbon dioxide
CVDs	cardiovascular diseases
Da	dalton
dH_2O	distilled water
DMEM	dulbecco's modified eagle medium
DNA	deoxyribonucleic acid

DPPH	2,2-diphenyl-1-picrylhydrazyl
DW	dry weight
EDTA	ethylenediaminetetraacetic acid
eV	electron volt
GAE	gallic acid equivalent
FDA	Food and Drug Administration
FID	flame ionization detector
Fig	figure
fl	femtoliters
FPP	fornesylpyrophosphate
FRAP	ferric-reducing antioxidant power
FRIM	Forest Research Institute Malaysia
FTC	ferric thiocyanate
g	gram
GAG	glcosoaminoglycans
GC-MS/MS	gas chromatography mass spectrometry
GGPP	geranylgeranyl pyrophosphate
g/L	gram per litre
GPx	glutathione peroxidase
HA	hyaluronan
Hb	haemoglobin
HCD	high cholesterol diet
HDL	high-density lipoprotein
H&E	hematoxylin and eosin

HMG-CoA	3-hydroxy-3-methylglutaryl-coenzyme A
HPLC	high performance liquid chromatography
IACUC	Institutional Animal Care and Use Committee
IC_{50}	inhibitory concentration 50%
ICAM -1	intercellular cell adhesion molecule-1
ICP-OES	inductively couple plasma-optical emission spectrometry
ID	inner diameter
IDL	intermediate density lipoprotein
IL	interleukin
kcal	kilocalorie
kg	kilogram
L	liter
LCAT	lecithin-cholesterol acyltransferase
LDL	low density lipoprotein
LOXs	lipoxygenases
LTB4	leukotriene B4
m	metre
mm	millimetre
mM	millimolar
mmol/l	millimol per litre
mg	milligram
mg/dl	milligram per deciliter
mg/kg	miligram per kilogram
mg/ml	milligram per milliliter

min	minute
ml	milliliter
ml/min	milliliter per minute
Mw	molecular weight
m/z	mass-to-charge ratio
NaCl	sodium chloride
nm	nanometer
NO	nitric oxide
OECD	Organization for Economic Cooperation and Development
O2-	superoxide
ONOO-	peroxynitrite
pg	pictogram
PGE2	prostaglandin E2
pH	*Puissance hyrogene*
ROS	reactive oxygen species
RP-HPLC	reverse phase-high performance liquid chromatography
rpm	revolution per minute
RT	retention time
s	second
SD	standard deviation
SOD	superoxide dismutase
SPSS	statistical package for social sciences
SRB	sulforhodamine B
SREBP	sterol regulatory element binding protein

TBA	thiobarbituric acid
TBIL	total bilirubin
TC	total cholesterol
TFC	total flavonoid content
TG	triglyceride
TPC	total phenolic content
µg	microgram
µg/ml	microgram per millilitre
µl	microlitre
U/l	unit per litre
Mm	micromolar
U/ml	unit per milliliter
µmol/l	micromol per litre
VCAM -1	vascular cell adhesion molecule-1
VLDL	very low density lipoprotein
v/v	volume per volume
WHO	World Health Organization
w/v	weight per volume

CHAPTER 1

INTRODUCTION

Hypercholesterolemia is known to play a crucial role in the development of atherosclerosis and is generally identified as a risk factor for cardiovascular diseases (CVDs), which is a primary cause of morbidity and mortality in most developed countries (Kaup *et al*., 2011; Vogel, 1997). Significant elevation of blood cholesterol can lead to the progression of fatty liver (Assy *et al.*, 2000) and renal injury (Quyyumi, 1998), as indicated by the increased levels of liver and kidney enzymes. Accumulation of cholesterol impairs endothelial dysfunction, which leads to low density lipoprotein (LDL) oxidation, vasoregulation, monocyte and platelet adhesion and smooth muscle cell proliferation (Shaila *et al*., 1995). Although several factors like lifestyle, age, improper diet and hypertension have been reported to cause heart failure (Schaefer *et al*., 1995), hypercholesterolemia due to elevated cholesterol level, mainly LDL (Krieger, 1998), is principally responsible for CVDs. Therefore, lowering the prevalence of hypercholesterolemia conditions is considered to be an essential therapeutic approach (Ali *et al*., 2000).

The current treatment for hypercholesterolemia is a synthetic drug, statins. Statins competitively inhibit HMG-CoA reductase, the enzyme that catalyzes the rate-limiting step in the biosynthesis of cholesterol. Basically, statins are well tolerated and effective in cholesterol lowering. The most common adverse effects of statins are liver and muscle toxicity (Bradford *et al*., 1991). This occurs due to increase of liver transaminases (greater than three-fold) in the body. If this happens, the statins therapy should be stopped; transaminases levels usually take about three months to return to the baseline (Maron *et al*., 2000). Another side effect of statins is myopathy, defined as muscle weakness or pain associated with the increased level of creatine kinase (CK) more than ten times the upper limit of normal. Symptoms may include increased serum concentration of the statin, malaise and fever. Acute renal failure and rhabdomyolysis may result if myopathy is not recognized and the drug is continued (Bellosta *et al*., 2004).

Due to the adverse effects of synthetic drugs, attention is now directed to alternative medicine of plant origin (Loke *et al*., 2010). Over the decades, the use of medicinal plants represents the interaction between human with the environment (Sasidharan *et al*., 2011). Medicinal plants have been widely reported on its medicinal properties, nutritional values and pharmacological activities like antioxidant, anti-thrombotic, anti-inflammatory, anti-atherogenic and cardioprotective effects (Manach *et al*., 2005). Medicinal plants that can inhibit or scavenge free radicals and reduce serum cholesterol have gained wide therapeutic benefits. Great efforts have been made to lower the risk of CVDs through the regulation of cholesterol, and the therapeutic effects of plants have been the main focus of many dietary studies (Zhang *et al*., 2007a; Prasad, 2005).

Accordingly, attempts were made to identify the antihypercholesterolemia effects of various medicinal plants. *B. alba* has been identified as a potent inhibitior of HMG-COA reductase. *B. alba* is known as Remayung locally, belongs to the family of Basellaceae. *B. alba* is a wildly cultivated vegetable that has been utilized for its various pharmacological activities such as antimicrobial, anti-ulcer, antimutagenic,

antihypertensive and many more (Adhikari *et al.*, 2012). Therefore, this study focuses on the potential of *B. alba* leaf extract as an alternative source of therapeutic against hypercholesterolemia and atherosclerosis. The specific objectives of this study were:

1) To screen the HMG COA reductase inhibitory activity of 25 medicinal plants.

2) To examine the phytochemical components of *B. alba* leaf methanol extract using Gas Chromatography Mass Spectrometry (GC-MS/MS) and Reverse Phase-High Performance Liquid Chromatography (RP-HPLC) analyses.

3) To evaluate the toxicity of *B. alba* leaf extract using cytotoxicity test on Vero and WRL-68 cell lines, acute and subchronic oral toxicity on rats.

4) To determine the antioxidant and anti-inflammatory activities, proximate and mineral composition, and heavy metal analysis of *B. alba* leaf extract.

5) To investigate the hypocholesterolemic and antiatherosclerotic effects of *B. alba* leaf extract in hypercholesterolemia-induced rabbits.

REFERENCES

Adair-Kirk, T. L. and Senior, R. M. (2008). Fragments of extracellular matrix as mediators of inflammation. *The International Journal of Biochemistry and Cell Biology* 40:1101-1110.

Adaramoye, O., Nwaneri, V., Anyanwu, K., Farombi, E. and Emerole, G. (2005). Possible anti-atherogenic effect of kolaviron (a *Garcinia kola* seed extract) in hypercholesterolemic rats. *Clinical and Experimental Pharmacology and Physiology* 32:40-46.

Adaramoye, O. A., Akintayo, O., Achem, J. and Fafunso, M. A. (2008). Lipid-lowering effects of methanolic extract of *Vernonia amygdalina* leaves in rats fed on high cholesterol diet. *Vascular Health and Risk Management* 4:235-241.

Adhikari, R., Naveen Kumar, H. and Shruthi, S. (2012). A review on medicinal importance of *Basella alba* L. *International Journal of Pharmaceutical Sciences and Drug Research* 4:110-114.

Ahmad, S. and Beigh, H. (2008). Ascorbic acid, carotenoid, total phenolic and antioxidant activity of various genotype of *B. alba*. *Journal of Medical Biol*ogical *Sciences* 3:1-8.

Ali, M., Al-Qattan, K., Al-Enezi, F., Khanafer, R. and Mustafa, T. (2000). Effect of allicin from garlic powder on serum lipids and blood pressure in rats fed with a high cholesterol diet. *Prostaglandins, Leukotrienes and Essential Fatty Acids* 62: 253-259.

Almandoz, J.P. (2015). Dietary supplements for cholesterol management in dyslipidemias (pp. 383-402). Humana Press.

Altmann, S.W., Davis, H.R. and Zhu, L.J. (2004). Niemann-Pick C1 like 1 protein is critical for intestinal cholesterol absorption. *Science* 303:1201-1214.

Alves, R., Casal, S., and Oliveira, M.B.P. (2009). Determination of vitamin E in coffee beans by HPLC using a micro-extraction method. *Food Science and Technology International* 15:57-63.

Amarenco, P., Bogousslavsky J. and Callahan A.S. (2003). Design and baseline characteristics of the stroke prevention by aggressive reduction in cholesterol levels (SPARCL) study. *Cerebrovascular Diseases* 16: 389-395.

Amic, D., Davidovic-Amic D., Beslo, D. and Trinajstic, N. (2010). Structure-radical scavenging activity relationships of flavonoids. *Croatica Chemica Acta* 76:55-61.

Anthony, M.S., Clarkson, T.B., Bullock, B.C. and Wagner, J.D. (1997). Soy protein versus soy phytoestrogens in the prevention of diet-induced coronary artery

atherosclerosis of male cynomolgus monkeys. *Arteriosclerosis, Thrombosis,* and *Vascular Biology* 17:2524-2531.

AOAC. 1997. Official methods of analysis of AOAC international (16th ed., 3rd revision).

Assmann, G. and Gotto, A.M. (2004). HDL cholesterol and protective factors in atherosclerosis. *Circulation* 109:8-14.

Assy, N., Kaita, K., Mymin, D., Levy, C., Rosser, B. and Minuk, G. (2000). Fatty infiltration of liver in hyperlipidemic patients. *Digestive Diseases and Sciences* 45:1929-1934.

Auletta, C. S. (1995). Acute, subchronic, and chronic toxicology. CRC Press, London.

Badellino, K.O., Wolfe, M.L. and Reilly, M.P. (2006). Endothelial lipase concentrations are increased in metabolic syndrome and associated with coronary atherosclerosis. *PLoS Medicine* e22.

Barzilai, N., Atzmon, G and Schechter, C. (2003). Unique lipoprotein phenotype and genotype associated with exceptional longevity. *JAMA: Journal of the American Medical Association* 290:2030-2040.

Bellosta, S., Paoletti, R. and Corsini, A. (2004). Safety of statins focus on clinical pharmacokinetics and drug interactions. *Circulation* 109:50-57.

Behrman, E.J. and Gopalan, V. (2005) Cholesterol and plants. *Journal of Chemical Education* 82:1791-1793.

Benn, M. (2009). Apolipoprotein B levels, APOB alleles and risk of ischemic cardiovascular disease in the general population, a review. *Atherosclerosis* 206:17-30.

Benn, M., Nordestgaard, B.G., Jensen, J.S. and Tybjarg-Hansen, A. (2007). Polymorphisms in apolipoprotein B and risk of ischemic stroke. *The Journal of Clinical Endocrinology and Metabolism* 92:3611-3617.

Benn, M., Nordestgaard, B.G. and Jensen, J.S. (2005). Polymorphism in APOB associated with increased low-density lipoprotein levels in both genders in the general population. *The Journal of Clinical Endocrinology and Metabolism* 90: 5797-5803.

Benzie, I. (2003). Evolution of dietary antioxidants. *Comparative Biochemistry and Physiology* 136:113-126.

Berge, K.E., Tian, H. and Grad, G.A. (2000). Accumulation of dietary cholesterol in sitosterolemia caused by mutations in adjacent ABC transporters. *Science* 290:1771-1775.

Bhatt, D.L. and Topol, E.J. (2002). Need to test the arterial inflammation hypothesis. *Circulation* 106:136-140.

Boekholdt, S.M., Souverein, O.W. and Tanck, M.T. (2006). Common variants of multiple genes that control reverse cholesterol transport together explain only a minor part of the variation of HDL cholesterol levels. *Clinical Genetics* 69:270-273.

Bolkent, S., Yanardag, R., Bolkent, S. and Döger, M. M. (2004). Beneficial effects of combined treatment with niacin and chromium on the liver of hyperlipemic rats. *Biological Trace Element Research* 101:219-229.

Borissoff, J.I., Spronk, H.M. and Cate, H. (2011). The hemostatic system as a modulator of atherosclerosis. *The New England Journal of Medicine* 364: 1746-1760.

Bradford, R.H., Shear, C.L., Chremos, A.N., Dujovne, C., Downton, M., Franklin, F.A. and Hurley, D.P. (1991). Expanded clinical evaluation of lovastatin (EXCEL) study results: I. Efficacy in modifying plasma lipoproteins and adverse event profile in 8245 patients with moderate hypercholesterolemia. *Archives of Internal Medicine* 151:43-49.

Brown, A.J., Sun, L. and Feramisco, J.D. (2002). Cholesterol addition to ER membranes alters conformation of SCAP, the SREBP Escort Protein that regulates cholesterol metabolism. *Molecular Cell* 10:237-245.

Brown, H.A. (2007). Lipodomics and bioactive lipids: mass spectrometry based lipid analysis, volume 432 (Methods in Enzymology). Boston, Academic Press.

Brown, K.M. and Arthur, J.R. (2001). Selenium, selenoproteins and human health: a review. *Public Health Nutrition* 4:593-599.

Brune, M., Rossander, L., and Hallberg, L. (1989). Iron absorption and phenolic compounds: importance of different phenolic structures. *European Journal of Clinical Nutrition* 43:547-557.

Busch, S.J., Chen, K.S., Parker, R.A., Wright, P.S. and Yates, M.T. (2000). Substituted phenols and thiophenols useful as antioxidant agents: Google patents.

Castellanos-Santiago, E and Yahia, E.M. (2008). Identification and quantification of betalains from the fruits of 10 Mexican prickly pear cultivars by high-performance liquid chromatography and electrospray ionization mass spectrometry. *Journal of Agricultural and Food Chemistry* 6:121-126.

Catalano, G, Duchene, E and Zélie, J. (2008). Cellular SR-BI and ABCA1-mediated cholesterol efflux are gender-specific in healthy subjects. *The Journal of Lipid Research* 49:635-643.

Catalgol, B. and Ozer, N. K. (2012). Protective effects of vitamin E against hypercholesterolemia-induced age-related diseases. *Genes and Nutrition* 7:91-98.

Cazarolli, L.H., Zanatta, L., Alberton, E.H., Figueiredo, M.S., Folador, P., Damazio, R.G. (2008). Flavonoids: Prospective drug candidates. *Mini-Reviews in Medicinal Chemistry* 8:1429-1440.

Chanet, A., Milenkovic, D., Deval, C., Potier, M., Constans, J., Mazur, A. and Berard, A.M. (2012). Naringin, the major grapefruit flavonoid, specifically affects atherosclerosis development in diet-induced hypercholesterolemia in mice. *The Journal of Nutritional Biochemistry* 23: 469-477.

Chirala, S and Wakil, S. (2004). Structure and function of animal fatty acid synthase. *Lipids* 39:1045-1053.

Cipollone, F., Mezzetti, A., Fazia, M.L., Cuccurullo, C., Iezzi, A., Ucchino, S. Stafforini, D.M. (2005). Association between 5-lipoxygenase expression and plaque instability in humans. *Arteriosclerosis, Thrombosis, and Vascular Biology* 25:1665-1670.

Choe, S.C., Kim, H.S., Jeong, T.S., Bok, S.H. and Park, Y.B. (2001). Naringin has an antiatherogenic effect with the inhibition of intercellular adhesion molecule-1 in hypercholesterolemic rabbits. *Journal of Cardiovascular Pharmacology* 38:947-955.

Cohen, J.C., Kiss, R.C., Pertsemlidis, A. (2004). Multiple rare alleles contribute to low levels of plasma HDL cholesterol. *Science* 305:869-872.

Cohen, J.C., Pertsemlidis, A. and Fahmi, S. (2006). Multiple rare variants in NPC1L1 associated with reduced sterol absorption and plasma low-density lipoprotein levels. *Proceedings of the National Academy of Sciences* USA 103:1810-1815.

Cohen, J., Pertsemlidis, A., Kotowski, I.K. (2005). Low LDL cholesterol in individuals of African descent resulting from frequent nonsense mutations in PCSK9. *Nature Genetics* 37:161-165.

Corella, D., Saiz, C. and Guillen, M. (2000). Association of TaqIB polymorphism in the cholesteryl ester transfer protein gene with plasma lipid levels in a healthy Spanish population. *Atherosclerosis* 152:367-376.

Corlett, J.L., Clegg, M.S., Keen, C.L and Grivetti, L.E. (2002). Mineral content of culinary and medicinal plants cultivated by Hmong refugees living in Sacramento, California. *International Journal of Food Sciences and Nutrition* 3: 23-34.

Costantino, L., Parenti, C., Di Bella, M., Zanoli, P. and Baraldi, M. (1993). Anti-inflammatory activity of newly synthesized 2,6-bis-(1,1-dimethylethyl) phenol derivatives. *Pharmacological Research* 27:349-358.

Cushnie, T.P. and Lamb, A.J. (2011). Recent advances in understanding the antibacterial properties of flavonoids. *International Journal of Antimicrobial Agents* 38:99-107.

Dashti, M., Kulik, W., Hoek, F., Veerman, E.C., Peppelenbosch, M.P. and Rezaee, F. (2011). A phospholipidomic analysis of all defined human plasma lipoproteins. *Scientific Reports* 1:139.

Davis, M., and Bredt, N. (1994). Renal methods for toxicity. *Principles and Methods of Toxicology*.

Deshmukh, S. and Gaikwad, D. (2013). A review of the taxonomy, ethnobotany, phytochemistry and pharmacology of *Basella alba* (Basellaceae). *Journal of Applied Pharmaceutical Science* 4:153-165.

Dusserre, E., Moulin, P. and Vidal H. (2000). Differences in mRNA expression of the proteins secreted by the adipocytes in human subcutaneous and visceral adipose tissues. *Biochimica et Biophysica Acta* 1500:88-96.

Duthie, G.G., Pedersen, M.W., Gardner, P.T., Morrice, P.C., Jenkinson, A.M., McPhail, D.B. and Steele, G.M. (1998). The effect of whisky and wine consumption on total phenol content and antioxidant capacity of plasma from healthy volunteers. *European Journal of Clinical Nutrition* 52:733-736.

Dybing, E., Doe, J., Groten, J., Kleiner, J., O'Brien, J., Renwick, A. and Walker, R. (2002). Hazard characterisation of chemicals in food and diet: dose response, mechanisms and extrapolation issues. *Food and Chemical Toxicology* 40:237-282.

Ebrahinzadeh, M., Ahmad, F. and Bekhradniz, R. (2008). Iron chelating activity, phenol
and flavonoid content of some medicinal plants, Iran. *African Journal of Biotechnology* 7:3188-3192.

Edeoga, H., Okwu, D. and Mbaebie, B. (2005). Phytochemical constituents of some Nigerian medicinal plants. *African Journal of Biotechnology* 4:685-688.

Eller, P., Schgoer, W. and Mueller, T. (2005). Hepatic lipase polymorphism and increased risk of peripheral arterial disease. *Journal of Internal Medicine* 258:34434-34438.

El-Qudah, J. (2008). Dietary intake of selected common vegetable foods and their total carotenoid determination. *American Journal of Agricultural and Biological Sciences* 3:729-733.

Endo, A. (2004). The origin of the statins. *Atherosclerosis Supplements* 5:125-130.

Evans, W.C. (2009). *Trease and Evans' pharmacognosy*: Elsevier Health Sciences.

Fasano, T., Cefalù, A.B. and Di Leo, E. (2007). A novel loss of function mutation of PCSK9 gene in white subjects with low-plasma low-density lipoprotein cholesterol. *Arteriosclerosis, Thrombosis and Vascular Biology* 27:677-681.

Feng, Z., Hao, W., Lin, X., Fan, D. and Zhou, J. (2014). Antitumor activity of total flavonoids from *Tetrastigma hemsleyanum* is associated with the inhibition of regulatory T cells in mice. *OncoTargets and Therapy*, 7:947-956.

Food and Drug Administration (FDA) (1993). *FDA Nutritional Labeling Manual: A Guide for Developing and Using Data Bases*. Washington DC: Food and Drug Administration, Center for Food Safety and Applied Nutrition.

Fotis, L., Agrogiannis, G., Vlachos, I.S., Pantopoulou, A., Margoni, A., Kostaki, M. and Perrea, D. (2012). Intercellular adhesion molecule (ICAM)-1 and vascular cell adhesion molecule (VCAM)-1 at the early stages of atherosclerosis in a rat model. *In Vivo* 26:243-250.

Frankel, E.N., Kanner, J., German, J.B., Parks, E. and Kinsella, J.E. (1993). Inhibition of oxidation of human low-density lipoprotein by phenolic substances in red wine. *Lancet* 341:454-457.

Friedman, M. (2007). Overview of antibacterial, antitoxin, antiviral and antifungal activities of tea flavonoids and teas. *Molecular Nutrition and Food Research* 51: 116-134.

Friesen, J.A. and Rodwell, V.W. (2004). The 3-hydroxy-3-methylglutaryl coenzyme-A (HMG-CoA) reductases. *Genome Biology* 5:248.

Frikke-Schmidt, R., Nordestgaard, B.G., Jensen, G.B. and Tybjaerg-Hansen, A. (2004). Genetic variation in ABC transporter A1 contributes to HDL cholesterol in the general population. *The Journal of Clinical Investigation* 114:1343-1353.

Fulda, S., Gorman, A. M., Hori, O. and Samali, A. (2010). Cellular stress responses: cell survival and cell death. *International Journal of Cell Biology* 214074.

Galeotti, F., Barile, E., Curir, P., Dolci, M. and Lanzotti, V. (2008). Flavonoids from carnation (*Dianthus caryophyllus*) and their antifungal activity. *Phytochemistry Letters* 1:44-48.

Garcia-Calvo, M., Lisnock, J. and Bull, H.G. (2005). The target of ezetimibe is Niemann Pick C1-Like 1 (NPC1L1). *Proceedings of the National Academy of Sciences* USA 102:8132-8137.

Gazzani, G., Papetti, A., Massolini, G. and Daglia, M. (2009). Anti and prooxidant activity of water soluble components of some common diet vegetables and the effect of thermal treatment. *Journal of Agricultural and Food Chemistry* 46: 4118-4122.

Geoghegan, K., Boyd, J. and Hoth, L. (2009). Binding to low density lipoprotein receptor accelerates futile catalytic cycling in PCSK9 and raises the equilibrium level of intramolecular acylenzyme. *Biochemistry* 48:2941-2949.

Gholamhoseinian, A., Sharifi-Far, F. and Shahouzehi, B. (2010). Inhibitory activity of some plant methanol extracts on 3-Hydroxy-3-Methylglutaryl coenzyme a reductase. *International Journal of Pharmacology* 6:705-711.

Giannini, E.G., Testa, R. and Savarino, V. (2005). Liver enzyme alteration: a guide for clinicians. *Canadian Medical Association Journal* 172:367-379.

Gibbons, G.F., Islam, K. and Pease, R.J. (2000). Mobilization of triacylglycerol stores. *Biochimica Biophysica Acta* 1483:37-57.

Globally Harmonized System of Classification and Labeling of Chemicals (GHS), 2005, Part 3: Health and Environmental Hazards, United States.

Goldstein, J.L., DeBose-Boyd, R.A. and Brown, M.S. (2006). Protein sensors for membrane sterols. *Cell* 124:35-46.

Gonzalez-Navarro, H., Nong, Z. and Freeman L. (2002). Identification of mouse and human macrophages as a site of synthesis of hepatic lipase. *The Journal of Lipid Research* 43:671-675.

Goodwin, B., Jones, S.A and Price, R.R. (2000). A regulatory cascade of the nuclear receptors FXR, SHP-1, and LRH-1 represses bile acid biosynthesis. *Molecular Cell* 6:517-526.

Gylling, H.M. and Miettinen, T.A. (2002). Inheritance of cholesterol metabolism of probands with high or low cholesterol absorption. *The Journal of Lipid Research* 43:1472-1476.

Haines, T.H. (2001). Do sterols reduce proton and sodium leaks through lipid bilayers?. *Progress in Lipid Research* 40:299-324.

Hall, J.E. (2010). *Guyton and Hall textbook of medical physiology*: Elsevier Health Sciences.

Halliwell, B. and Gutteridge, J. (2007), *Free radical in biochemistry and medicine*. Oxford university press.

Harborne, J.B. (1984). *Phytochemical methods* 278: Springer.

Hartig, K. and Beck, E. (2005). Assessment of lovastatin application as tool in probing cytokinin-mediated cell cycle regulation. *Physiologia Plantarum* 125:260-267.

Harwood, H.J., Chandler, C.E., Pellarin, L.D., Bangerter, F., Wilkins, R., Long, C. and Pettini, J. (1993). Pharmacologic consequences of cholesterol absorption inhibition: alteration in cholesterol metabolism and reduction in plasma cholesterol concentration induced by the synthetic saponin beta-tigogenin cellobioside (CP-88818; tiqueside). *Journal of Lipid Research* 34:377-395.

Hebbachi, A.M. and Gibbons, G.F. (2001). Microsomal membrane-associated apoB is the direct precursor of secreted VLDL in primary cultures of rat hepatocytes. *The Journal of Lipid Research* 42:1609-1617.

Hendra, R., Ahmad, S., Oskoueian, E., Sukari, A. and Shukor, M.Y. (2011). Antioxidant, anti-inflammatory and cytotoxicity of *Phaleria macrocarpa* (Boerl.) scheff fruit. *BMC Complementary and Alternative Medicine* 11:110.

Hermann, M., Bogsrud, M.P., Molden, E., Asberg, A., Mohebi, B.U., Ose, L. and Retterstøl, K. (2006). Exposure of atorvastatin is unchanged but lactone and acid metabolites are increased several-fold in patients with atorvastatin-induced myopathy. *Clinical Pharmacology and Therapeutics* 79:532-539.

Hernández, F., Portolés, T., Pitarch, E., López, F. J., Beltrán, J. and Vázquez, C. (2005). Potential of gas chromatography coupled to triple quadrupole mass spectrometry for quantification and confirmation of organohalogen xenoestrogen compounds in human breast tissues. *Analytical Chemistry* 77:7662-7672.

Higdon, J., Drake, V. and Frei, B. (2009). Non-antioxidant roles for dietary flavonoids: reviewing the relevance to cancer and cardiovascular diseases. *Nutraceuticals World*. Rodman Media.

Hodzic, Z., Pasalic, H., Memiseric, A., Srabovic, M. and Saletovic M. (2008). The influence of total phenolic content on antioxidant capacity in the *B. alba*. *European Journal of Scientific Research* 28:471-477.

Hollman, P.C., Hertog, M.G. and Katan, M.B. (1996). Role of dietary flavonoids in protection against cancer and coronary heart disease. *Biochemical Society Transactions* 24:785-789.

Homer, V.M., Marais, A.D. and Charlton F (2008). Identification and characterization of two non-secreted PCSK9 mutants associated with familial hypercholesterolemia in cohorts from New Zealand and South Africa. *Atherosclerosis* 196:659-666.

Hooper, A.J., Tran, H.A, Formby, M.R. and Burnett, J.R. (2008). A novel missense LIPA gene mutation, N98S, in a patient with cholesteryl ester storage disease. *Clinica Chimica Acta* 398:152-154.

Hölzl, G. and Dörmann, P. (2007). Structure and function of glycoglycerolipids in plants and bacteria. *Progress in Lipid Research* 46:225-243.

Horton, J.D., Goldstein, J.L. and Brown, M.S. (2002). SREBPs: activators of the complete program of cholesterol and fatty acid synthesis in the liver. *Journal of Clinical Investigation* 109:1125-1131.

Horton, J.D., Shah, N.A. and Warrington, J.A. (2003). Combined analysis of oligonucleotide microarray data from transgenic and knockout mice identifies

direct SREBP target genes. *Proceedings of the National Academy of Sciences USA* 100:12027-12032.

Hostettmann, K. and Marston, A. (2005). *Saponins*: Cambridge University Press.Hotz, C. and Gibson, R.S. (2007). Traditional food-processing and preparation practices to enhance the bioavailability of micronutrients in plant-based diets. *The Journal of Nutrition* 137:1097-1100.

Hovingh, G.K., Groot, E. and Steeg, W. (2005). Inherited disorders of HDL metabolism and atherosclerosis. *Current Opinion in Lipidology* 16:139-145.

Ismail, H.I., Chan, K.W., Mariod, A.A. and Ismail, M. (2010a). Phenolic content and antioxidant activity of cantaloupe (*Cucumis melo*) methanolic extracts. *Food Chemistry* 119:643-647.

Ismail, M., Al-Naqeep, G. and Chan, K.W. (2010b). *Nigella sativa* thymoquinone-rich fraction greatly improves plasma antioxidant capacity and expression of antioxidant genes in hypercholesterolemic rats. *Free Radical Biology and Medicine* 48:664-672.

Ismail, M.F., Gad, M.Z. and Hamdy, M.A. (1999). Study of the hypolipidemic properties of pectin, garlic and ginseng in hypercholesterolemic rabbits. *Pharmacological Research* 39:157-166.

Jan, N., Göran K.H. and Prediman K.S. (2005). Immunomodulation of atherosclerosis-implications for vaccine development-ATVB in focus. *Arteriosclerosis, Thrombosis, and Vascular Biology* 5:18-28.

Jeon, S.M., Park, Y.B. and Choi, M.S. (2004). Antihypercholesterolemic property of naringin alters plasma and tissue lipids, cholesterol-regulating enzymes, fecal sterol and tissue morphology in rabbits. *Clinical Nutrient* 23:1025-1034.

Jeong, Y.J., Choi, Y.J., Choi, J.S., Kwon, H.M., Kang, S.W., Bae, J.Y. and Kang, Y.H. (2007). Attenuation of monocyte adhesion and oxidised LDL uptake in luteolin-treated human endothelial cells exposed to oxidised LDL. *British Journal of Nutrition* 97:447-457.

Johnson, J.H. and Jensen, J.M. (1998). Hepatotoxicity and secondary photosensitization in a red kangaroo (*Megaleia rufus*) due to ingestion of *Lantana camara*. *Journal of Zoo and Wildlife Medicine* 29:203-207.

Jothy, S.L., Zakaria, Z., Chen, Y., Lau, Y.L., Latha, L.Y. and Sasidharan, S. (2011). Acute oral toxicity of methanolic seed extract of *Cassia fistula* in mice. *Molecules* 16:5268-5282.

Jung, K.A., Song, T.C., Han, D., Kim, I.H., Kim, Y.E. and Lee, C.H. (2005). Cardiovascular protective properties of kiwifruit extracts *in vitro*. *Biological and Pharmaceutical Bulletin* 28:1782-1785.

Kajinami, K., Takekoshi, N. and Saito, Y. (2003). Pitavastatin: efficacy and safety profiles of a novel synthetic HMG-CoA reductase inhibitor. *Cardiovascular Drug Reviews* 21:199-215.

Kaup, S.R., Arunkumar, N., Bernhardt, L.K., Vasavi, R.G., Shetty, S.S., Pai, S.R. and Arunkumar, B. (2011). Antihyperlipedemic activity of *Cynodon dactylon* extract in high-cholesterol diet fed wistar rats. *Genomic Medicine, Biomarkers, and Health Sciences* 3:98-102.

Kennedy, G.L., Ferenz, R.L. and Burgess, B.A. (1986). Estimation of acute oral toxicity in rats by determination of the approximate lethal dose rather than the LD50. *Journal of Applied Toxicology* 6:145-148.

Kerry, N.L., and Abbey, M. (1997). Red wine and fractionated phenolic compounds prepared from red wine inhibit low density lipoprotein oxidation *in vitro*. *Atherosclerosis* 135:93-102.

Khosla, U.M., Zharikov, S., Finch, J.L., Nakagawa, T., Roncal, C., Mu, W. and Johnson, R.J. (2005). Hyperuricemia induces endothelial dysfunction. *Kidney International* 67:1739-1742.

Khatun, K., Mahtab, H., Khanam, P.A., Sayeed, M.A. and Khan, K.A. (2007). Oyster mushroom reduced blood glucose and cholesterol in diabetic subjects. *Mymensingh Medical Journal* 16:94-99.

Kim, S.Y., Kim, H.J., Lee, M.K., Jeon, S.M., Do, G.M., Kwon, E.Y. and Park, Y.B. (2006). Naringin time-dependently lowers hepatic cholesterol biosynthesis and plasma cholesterol in rats fed high-fat and high-cholesterol diet. *Journal of Medicinal Food* 9:582-586.

King, C.R., Knutson, K.l., Rathouz, P.J., Sidney, S., Liu, K. and Lauderdale, D.S. (2008). Short sleep duration and incident coronary artery calcification. *JAMA: Journal of the American Medical Association* 300:2859-2866.

Klaassen, C.D. (2013). *Casarett and Doull's Toxicology: The basic science of poisons* (Vol. 1236): McGraw-Hill New York.

Koedrith, P., Kim, H., Weon, J.I. and Seo, Y.R. (2013). Toxicogenomic approaches for understanding molecular mechanisms of heavy metal mutagenicity and carcinogenicity. *International Journal of Hygiene and Environmental Health* 216:587-598.

Krieger, M. (1998). The "best" of cholesterols, the "worst" of cholesterols: a tale of two receptors. *Proceedings of the National Academy of Sciences* 95:4077-4080.

Kris-Etherton, P.M., Hecker, K.D., Bonanome, A., Coval, S.M., Binkoski, A.E., Hilpert, K.F. and Etherton, T.D. (2002). Bioactive compounds in foods: their role in the prevention of cardiovascular disease and cancer. *American Journal of Medicine,* 113:71s-88s.

Kris-Etherton, P.M. and Keen, C.L. (2002). Evidence that the antioxidant flavonoids in tea and cocoa are beneficial for cardiovascular health. *Current Opinion in Lipidology* 13:41-49.

Kuete, V., Krusche, B., Youns, M., Voukeng, I., Fankam, A.G., Tankeo, S. and Efferth, T. (2011). Cytotoxicity of some Cameroonian spices and selected medicinal plant extracts. *Journal of Ethnopharmacology* 134:803-812.

Kumar, P. (2010). Indian spinach, *Basella alba* (PUI) succulent, branched, smooth, twining herbaceous vine. *Best Nutrition*. (PR Log-Global Press Release Distribution).

Kumar, S., Malhotra, R. and Kumar, D. (2010). Antidiabetic and free radicals scavenging potential of *Euphorbia hirta* flower extract. *Indian Journal of Pharmaceutical Sciences* 72:533-539.

Kumar, V., Bhat, Z., Kumar, D., Bohra, P. and Sheela, S. (2011a). *In-vitro* anti-inflammatory activity of leaf extracts of *Basella alba* linn. Var. alba. *International Journal of Drug Development and Research* 3:176-179.

Kumar, V., Butcher, S., Öörni, J. and Katariina, E.(2011b). Three-dimensional cryoEM reconstruction of native LDL particles to 16Å resolution at physiological body temperature. *PLoS ONE* 6:e18841.

Kumaravel, S. and Alagusundaram, K. (2014). Determination of mineral content in Indian spices by ICP-OES. *Oriental Journal of Chemistry* 30:112-118.

Kureishi, Y., Luo, Z., Shiojima, I., Bialik, A., Fulton, D., Lefer, D.J. and Walsh, K. (2000). The HMG-CoA reductase inhibitor simvastatin activates the protein kinase Akt and promotes angiogenesis in normocholesterolemic animals. *Nature Medicine* 6:1004-1010.

Kuzuyama, T., and Seto, H. (2003). Diversity of the biosynthesis of the isoprene units. *Natural Product Reports* 20:171-183.

Lagace, T.A., Curtis, D.E. and Garuti R. (2006). Secreted PCSK9 decreases the number of LDL receptors in hepatocytes and in livers of parabiotic mice. *Journal of Clinical Investigation* 116:2995-3005.

Lai, X.F., Qin, H.D., Guo, L.L., Luo, Z.G., Chang, J. and Qin, C.C. (2014). Hypercholesterolemia increases the production of leukotriene B4 in neutrophils by enhancing the nuclear localization of 5-Lipoxygenase. *Cellular Physiology and Biochemistry* 34:1723-1732.

Larson R. (2013). The antioxidants of higher plants. *Phytochemistry* 27:969-978.

Lasekan, O. (2013). Volatile constituents of roasted tigernut oil (*Cyperus esculentus* L.). *Journal of Science and Food Agriculture* 93:1055-1061.

Lasekan, O., Buettner, A., and Christlbauer, M. (2007). Investigation of important odorants of palm wine (*Elaeis guineensis*). *Food Chemistry* 105:15-23.

Lecerf, J.M. and de Lorgeril, M. (2011). Dietary cholesterol: from physiology to cardiovascular risk. *British Journal of Nutrition* 106:6-14.

Lee, J., Park, C., Kim, H., Hwang, S. and Chung, W. (2002). Single dose toxicity study of Hwangjaegongjinbo, an invigorator, in mice and rats. *Journal of Toxicology and Public Health* 18:73-77.

Lee, S.J., Choi, E.K., Seo, K.W., Bae, J.U., Kim, Y.H., Park, S.Y. and Kim, C.D. (2013). 5-Lipoxygenase plays a pivotal role in endothelial adhesion of monocytes via an increased expression of Mac-1. *Cardiovascular Research*, cvt135.

Lee, S.J., Umano, K., Shibamoto, T. and Lee, K.G. (2005). Identification of volatile components in basil (*Ocimum basilicum* L.) and thyme leaves (*Thymus vulgaris* L.) and their antioxidant properties. *Food Chemistry* 91:131-137.

Lewington, S., Whitlock, G., Clarke, R., Sherliker, P., Emberson, J. and Halsey, J. (2007). Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55,000 vascular deaths. *Lancet* 370:1829-1839.

Liadaki, K.N., Liu, T., and Xu, S. (2000). Binding of high density lipoprotein (HDL) and discoidal reconstituted HDL to the HDL receptor scavenger receptor class B type I. *Journal of Biological Chemistry* 275:21262-21271.

Liao, J.K. and Laufs, U. (2005). Pleiotropic effects of statins. *Annual Review of Pharmacology and Toxicology* 45:89-118.

Lin, S., Sherliker, P. and Halsey (2010). Structural identification and bioactivities of red-violet pigments present in *Basella alba* fruits. *Journal Agriculture Food Chemistry* 10:456- 461.

Ling, W.H., Cheng, Q.X., Ma, J. and Wang, T. (2011). Red and black rice decrease atherosclerotic plaque formation and increase antioxidant status in rabbits. *Journal of Nutrition* 131:1421-1426.

Liu, R.H. (2004). Potential synergy of phytochemicals in cancer prevention: mechanism of action. *Journal of Nutrition* 134:3479s-3485s.

Loke, W.M., Proudfoot, J.M., Hodgson, J.M., McKinley, A.J., Hime, N., Magat, M. and Croft, K.D. (2010). Specific dietary polyphenols attenuate atherosclerosis in apolipoprotein E-knockout mice by alleviating inflammation and

endothelial dysfunction. *Arteriosclerosis, Thrombosis and Vascular Biology* 30:749-757.

Lloyd-Jones, D., Adams, R. and Carnethon, M. (2009). Heart disease and stroke statistics--2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* 119:480–486.

Ma, X., Li, Y.F., Gao, Q., Ye, Z.G., Lu, X.J., Wang, H.P. and Xia, Q. (2008). Inhibition of superoxide anion-mediated impairment of endothelium by treatment with luteolin and apigenin in rat mesenteric artery. *Life sciences* 83:110-117.

Madhesh, M. and Vaiyapuri, M. (2013). Luteolin a dietary flavonoid attenuates isoproterenol-induced myocardial oxidative stress in rat myocardium: An *in vivo* study. *Biomedicine and Preventive Nutrition* 3:159-164.

Mahan, L.K., Escott-Stump, S., Raymond, J.L. and Krause, M.V. (2012). Krause's food and the nutrition care process. St. Louis, Mo: Elsevier/Saunders.

Mahley, R.W. and Rall, S.C. (2000). Apolipoprotein E: far more than a lipid transport protein. *Annual Review of Genomics and Human Genetics* 1:507-537.

Manach, C., Mazur, A. and Scalbert, A. (2005). Polyphenols and prevention of cardiovascular diseases. *Current Opinion in Lipidology* 16:77-84.

Manach, C., Scalbert, A., Morand, C., Rémésy, C. and Jiménez, L. (2004). Polyphenols: food sources and bioavailability. *The American Journal of Clinical Nutrition*, 79:727-747.

Manner, S., Skogman, M., Goeres, D., Vuorela, P. and Fallarero, A. (2013). Systematic exploration of natural and synthetic flavonoids for the inhibition of *Staphylococcus aureus* biofilms. *International Journal of Molecular Sciences* 14: 19434-19451.

Maron, D.J., Fazio, S., and Linton, M.F. (2000). Current perspectives on statins. *Circulation* 101:207-213.

Marschall, H.U. and Einarsson, C. (2007). Gallstone disease. *Journal of International Medicine* 261:529-542.

Martinello, F., Soares, S., Franco, J., Santos, A., Sugohara, A., Garcia, S. and Uyemura, S. (2006). Hypolipemic and antioxidant activities from *Tamarindus indica* L. pulp fruit extract in hypercholesterolemic hamsters. *Food and Chemical Toxicology* 44:810-818.

Martinet, W. and Knaapen, M. (2002). Oxidative DNA damage and repair in experimental atherosclerosis are reversed by dietary lipid lowering. *Circulation Research* 88:733-739.

Mashaghi, S., Jadidi, T., Koenderink, G. and Mashaghi, A. (2013). Lipid nanotechnology. *International Journal of Molecular Science* 14:4242-4282.

Matsuura, H. (2001). Saponins in garlic as modifiers of the risk of cardiovascular disease. *The Journal of Nutrition* 131:1000S-1005S.

Mattill, H. (2011). Antioxidants. *Annual Review of Biochemistry* 16: 177–218.Mohammed, H.K.P., Abraham, A., Saraswathi, R., Mohanta, G.P. and Nayar, C. (2012). Formulation and evaluation of herbal gel of *Basella alba* for wound healing activity. *Journal of Pharmaceutical Sciences and Research* 4: 1642-1648.

McAnlis, G.T., McEneny, J., Pearce, J., and Young, I.S. (1999). Absorption and antioxidant effects of quercetin from onions, in man. *Europen Journal Clinical Nutrion* 53:92-96.

McCoy, M.G., Sun, G.S. and Marchadier, D. (2002). Characterization of the lipolytic activity of endothelial lipase. *Journal of Lipid Research* 43:921-929.

Meda, A., Lamien, C.E., Romito, M., Millogo, J. and Nacoulma, O.G. (2005). Determination of the total phenolic, flavonoid and proline contents in Burkina Fasan honey, as well as their radical scavenging activity. *Food Chemistry* 93: 571-577.

Mekhfi, H., ElHaouari, M., Bnouham, M., Aziz, M., Ziyyat, A. and Legssyer, A. (2006). Effects of extracts and tannins from *Arbutus unedo* leaves on rat platelet aggregation. *Phytotherapy Research* 20:135-139.

Miyake, Y., Kimura, R. and Kokubo, Y. (2008). Genetic variants in PCSK9 in the Japanese population: rare genetic variants in PCSK9 might collectively contribute to plasma LDL cholesterol levels in the general population. *Atherosclerosis* 196:29-36.

McCrindle, B.W., Ose, L. and Marais, A.D. (2003). Efficacy and safety of atorvastatin in children and adolescents with familial hypercholesterolemia or severe hyperlipidemia: a multicenter, randomized, placebo-controlled trial. *Journal of Pediatric* 143:74-80.

Moss, A.J. (1991). Cholesterol and Atherosclerosis: Diagnosis and Treatment. *JAMA Journal of the American Medical Association* 266:2910-2911.

Moundipa, F.P., Bnouham, L.M. and Rao, N.B. (2011). Effects of aqueous extracts of *Hibiscus macranthus* and *Basella alba* in mature rat testis function. *Journal of Ethnopharmacology* 11:65-72.

Moundipa, P., Salvati, S. and Marais, A.D. (2005). Effects of *Basella alba* and *Hibiscus macranthus* extracts on testosterone production of adult rat and bull Leydig cells. *Asian Journal of Andrology* 3:23-34.

Mukhtar, R.Y.A., Reid, J. and Reckless, J.P.D. (2005). Pitavastatin. *International Journal of Clinical Practice* 59:239-252.

Naci, H., Brugts, J. and Ades, T. (2013). Comparative tolerability and harms of individual statins: a study-level network meta-analysis of 246 955 participants from 135 randomized, controlled trials. *Circulation: Cardiovascular Quality and Outcomes* 6:390-399.

Napoli, C. and Lerman, L.O. (2010) Involvement of oxidation-sensitive mechanisms in the cardiovascular effects of hypercholesterolemia. *Mayo Clinic Proceedings.* 76:619-631.

Natali, F., Siculella, L., Salvati, S. and Gnoni, G.V. (2007). Oleic acid is a potent inhibitor of fatty acid and cholesterol synthesis in C6 glioma cells. *Journal of Lipid Research* 48:1966-1975.

National Cholesterol Education Program (NCEP). (2001). Executive summary of the third report of the NCEP expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III) *JAMA: Journal of the American Medical Association* 285:2486-2497.

Newman, D.J., Cragg, G.M. and Snader, K.M. (2003). Natural products as sources of new drugs over the period 1981-2002. *Journal of Natural Products* 66:1022-1037.

Nijveldt, R.J., Van Nood, E.L.S., Van Hoorn, D.E., Boelens, P.G., Van Norren, K., and Van Leeuwen, P.A. (2001). Flavonoids: a review of probable mechanisms of action and potential applications. *The American Journal of Clinical Nutrition* 74:418-425.

Nissen, S.E., Nicholls, S.J., Sipahi, I., Libby, P., Raichlen, J.S., Ballantyne, C.M., Davignon, J., Erbel, R., Fruchart, J.C., Tardif, J.C., Schoenhagen, P., Crowe, T., Cain, V., Wolski, K., Goormastic, M. and Tuzcu, E.M. (2006). Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial. *Journal of the American Medical Association* 295:1556-1565.

Nofer, J.R., Kehrel, B., Fobker, M., Levkau, B., Assmann, G. and von Eckardstein, A. (2002). HDL and arteriosclerosis: beyond reverse cholesterol transport. *Atherosclerosis* 161:1-16.

Nohturfft, A., Tabe, D. and Goldstein, J.L.(2000). Regulated step in cholesterol feedback localized to budding of SCAP from ER membranes. *Cell* 102:315-323.

O'Byrne, D.J., Devaraj, S., Grundy, S.M. and Jialal, I. (2002). Comparison of the antioxidant effects of Concord grape juice flavonoids α-tocopherol on markers of oxidative stress in healthy adults. *The American Journal of Clinical Nutrition* 76:1367-1374.

Organization of Economic Co-operation and Development (OECD). (1994). *The OECD Guidelines for the Testing of Chemicals*: *420 Acute Oral Toxicity- Fixed Dose Procedure*, Paris, France.

Organization of Economic Co-operation and Development (OECD). (1997). *The OECD Guidelines for the Testing of Chemicals*: *408 Subchronic Oral Toxicity- Rodent: 90-Days Study Procedure*, Paris, France.

Ogata, N., Fujimori, S., Oka, Y. and Kaneko, K. (2010). Effects of three strong statins (atorvastatin, pitavastatin, and rosuvastatin) on serum uric acid levels in dyslipidemic patients. *Nucleosides, Nucleotides and Nucleic Acids* 29:321-324.

Ogunlesi, M., Okiei, W. and Osibote, E.A. (2010). Analysis of the essential oil from the leaves of *Sesamum radiatum*, a potential medication for male infertility factor by gas chromatography-mass spectrometry. *African Journal of Biotechnology* 9:1060-1067.

Ohvo-Rekilä, H., Ramstedt, B., Leppimäki, P. and Slotte J.P. (2002). Cholesterol interactions with phospholipids in membranes. *Progress in Lipid Research* 41: 66-97.

Olson, H., Betton, G., Robinson, D., Thomas, K., Monro, A., Kolaja, G. and Bracken, W. (2000). Concordance of the toxicity of pharmaceuticals in humans and in animals. *Regulatory Toxicology and Pharmacology* 32:56-67.

Ordovas, J.M., Cupples, A. and Corella, D. (2000). Association of cholesteryl ester transfer protein-TaqIB polymorphism with variations in lipoproteins subclasses and coronary heart disease risk. *Arteriosclerosis, Thrombosis, and Vascular Biology* 20:1323-1329.

Organization, W.H. (2002). WHO traditional medicine strategy 2002-2005.

Ou B., Huang, D., Hampsch-Woodill, M., Flanagan, J. and Deemer, E. (2002). Analysis of antioxidant activities of common vegetables employing oxygen radical absorbance capacity (ORAC) and ferric reducing antioxidant power (FRAP) assays: a comparative study. *Journal of Agriculture and Food Chemistry* 50: 3122-3128.

Out, R., Hoekstra, M. and Spijkers, J.A. (2004). Scavenger receptor class B type I is solely responsible for the selective uptake of cholesteryl esters from HDL by the liver and the adrenals in mice. *Journal of Lipid Research* 45:2088-2095.

Oyewole, O.A. and Kalejaiye, O.A. (2012). The antimicrobial activities of ethanolic extracts of *Basella alba* on selected microorganisms. *Scientific Journal of Microbiology* 1:113-118.

Ozaki, K., Kubo, T., Imaki, R., Shinagawa, H., Fukaya, H., Ohtaki, K., Ozaki, S., Izumi, T. and Aizawa, Y. (2006). The anti-atherosclerotic effects of lipid lowering with atorvastatin in patients with hypercholesterolemia. *Journal of Atherosclerosis Thrombosis* 13:216-219.

Özer, N.K., Negis, Y., Aytan, N., Villacorta, L., Ricciarelli, R., Zingg, J.M. and Azzi, A. (2006). Vitamin E inhibits CD36 scavenger receptor expression in hypercholesterolemic rabbits. *Atherosclerosis* 184:15-20.

Ozer, N.K., Palozza, P., Boscoboinik, D. and Azzi, A. (1993). d-alpha-Tocopherol inhibits low density lipoprotein induced proliferation and protein kinase C activity in vascular smooth muscle cells. *FEBS Letters* 322:307-310.

Parker, R.A., Sabrah, T., Cap, M. and Gill, B.T. (1995). Relation of vascular oxidative stress, α-tocopherol, and hypercholesterolemia to early atherosclerosis in hamsters. *Arteriosclerosis, Thrombosis, and Vascular Biology* 15:349-358.

Patel, S., Gheewala, N., Suthar, A. and Shah, A. (2009). *In-vitro* cytotoxicity activity of *Solanum nigrum* extract against Hela cell line and Vero cell line. *International Journal of Pharmacy and Pharmaceutical Sciences* 1:38-46.

Pietta, P. (2009). Flavonoids as antioxidants. *Journal of Natural Products* 63:1035-1042.

Pin, K., Chuah, A.L., Rashih, A.A., Mazura, M., Fadzureena, J., Vimala, S. and Rasadah, M. (2010). Antioxidant and anti-inflammatory activities of extracts of betel leaves (*Piper betle*) from solvents with different polarities. *Journal of Tropical Forest Science* 22:448-455.

Pina, E.M., Araújo, F.W., Souza, I.A., Bastos, I.V., Silva, T.G., Nascimento, S. and Melo, S.J. (2012). Pharmacological screening and acute toxicity of bark roots of *Guettarda platypoda*. *Revista Brasileira de Farmacognosia* 22:1315-1322.

Ping, K., Darah, I., Chen, Y., Sreeramanan, S. and Sasidharan, S. (2013). Acute and subchronic toxicity study of *Euphorbia hirta* L. methanol extract in rats. *BioMed Research International* 182064.

Ping, K., Darah, I., Yusuf, U. K., Yeng, C. and Sasidharan, S. (2012). Genotoxicity of *Euphorbia hirta*: An *Allium cep*a assay. *Molecules* 17:7782-7791.

Poeckel, D. and Funk, C.D. (2010). The 5-lipoxygenase/leukotriene pathway in preclinical models of cardiovascular disease. *Cardiovascular Research* cvq016.

Pour, B.M., Latha, L.Y. and Sasidharan, S. (2011). Cytotoxicity and oral acute toxicity studies of *Lantana camara* leaf extract. *Molecules* 16:3663-3674.

Prasad, K. (2005). Hypocholesterolemic and antiatherosclerotic effect of flax lignan complex isolated from flaxseed. *Atherosclerosis* 172:269-275.

Premalatha, B., and Rajgopal, G. (2005). Cancer-an ayurvedic perspective. *Pharmacology Research* 51:19-30.

Pullinger, C.R., Eng, C. and Salen, G. (2002). Human cholesterol 7alpha-hydroxylase (CYP7A1) deficiency has a hypercholesterolemic phenotype. *Journal of Clinical Investigation* 110:109-117.

Qin, S., Kawano, K. and Bruce, C. (2000). Phospholipid transfer protein gene knock-out mice have low high density lipoprotein levels, due to hypercatabolism, and accumulate apoA-IV -rich lamellar lipoproteins. *Journal of Lipid Research* 41:269-276.

Queiroz, K.C, Tio, R.A., Zeebregts, C.J., Bijlsma, M.F., Zijlstra, F., Badlou, B., de Vries M., Ferreira, C.V., Spek, C.A., Peppelenbosch, M.P. and Rezaee, F. (2010). Human plasma very low density lipoprotein carries. *Journal of Proteome Research* 9:6052-6059.

Quyyumi, A.A. (1998). Endothelial function in health and disease: new insights into the genesis of cardiovascular disease. *The American Journal of Medicine* 105:32S-39S.

Rahman, M., Rahman, M., Rahman, M., Shadli, S.M. and Alam M.F., (2008). Free radical scavenging activity and phenolic content of *Cassia sophera L. African. Journal Biotech*nology 7:1591-1593.

Ranawat, L., Bhatt, J. and Patel, J. (2010). Hepatoprotective activity of ethanolic extracts of bark of *Zanthoxylum armatum* DC in CCl_4 induced hepatic damage in rats. *Journal of Ethnopharmacology* 127:777-780.

Rao, A.V. and Rao, L.G. (2007). Carotenoids and human health. *Pharmacological Research* 55:207-216.

Raza, M., Al-Shabanah, O., El-Hadiyah, T. and Al-Majed, A. (2002). Effect of prolonged vigabatrin treatment on hematological and biochemical parameters in plasma, liver and kidney of Swiss albino mice. *Scientia Pharmaceutica* 70:135-145.

Reed, J. (2002). Cranberry flavonoids, atherosclerosis and cardiovascular health. *Critical Reviews in Food Science and Nutrition* 42:301-316.

Rein, D., Paglieroni, T.G., Wun, T., Pearson, D.A., Schmitz, H.H., Gosselin, R. and Keen, C. . (2000). Cocoa inhibits platelet activation and function. *The American Journal of Clinical Nutrition* 72:30-35.

Rodrigues, H., Diniz, Y., Faine, L., Galhardi, C., Burneiko, R., Almeida, J. and Novelli, E. (2005). Antioxidant effect of saponin: potential action of a soybean flavonoid on glucose tolerance and risk factors for atherosclerosis. *International Journal of Food Sciences and Nutrition* 56:7985.

Ryu, S.D., Park, C.S., Baek, H.M., Baek, S.H., Hwang, S.Y. and Chung, W.G. (2004). Anti-diarrheal and spasmolytic activities and acute toxicity study of Soonkijangquebo, a herbal anti-diarrheal formula. *Journal of Ethnopharmacology* 91:75-80.

Rudi, H., Syahida, A., Ehsan, O., Aspollah, S.and Yunus, S. (2011). Antioxidant, Anti-inflammatory and Cytotoxicity of *Phaleria macrocarpa* (Boerl.) Scheff Fruit. *BMC Complementary and Alternative Medicine* 11:110.

Russell D.W. (2009). Fifty years of advances in bile acid synthesis and metabolism. *Journal of Lipid Research* 50:S120-S125.

Sadava, D., Hillis, D.M., Heller, H.C. and Berenbaum, M.R. (2011). Life: The Science of Biology 9th Edition. San Francisco: Freeman. pp. 105-114.

Saddoughi, S.A., Song, P. and Ogretmen, B. (2008). Roles of bioactive sphingolipids in cancer biology and therapeutics. *Subcellular Biochemistry* 49:413-440.

Sakuma, N., Yoshikawa, M., Hibino, A., Sato, A., Kamiya, Y., Ohte, N. and Inoue, M. (2001). Ascorbic acid protects against peroxidative modification of low-density lipoprotein, maintaining its recognition by LDL receptors. *Journal of Nutritional Science and Vitaminology* 47:28-31.

Salah, N., Miller, N.J., Paganga, G., Tijburg, L., Bolwell, G.P. and Riceevans, C. (1995). Polyphenolic flavanols as scavengers of aqueous phase radicals and as chain-breaking antioxidants. *Archives of Biochemistry and Biophysics* 322:339-346.

Salvamani, S., Gunasekaran, B., Shaharuddin, N. A., Ahmad, S. A., and Shukor, M. Y. (2014). Antiartherosclerotic effects of plant flavonoids. *BioMed Research International* 480258.

Samyn, H., Moerland, M. and van Gent T. (2009). Elevation of systemic PLTP, but not macrophage-PLTP, impairs macrophage reverse cholesterol transport in transgenic mice. *Atherosclerosis* 204:429-434.

Sanhueza, J., Valdes, J., Campos, R., Garrido, A., and Valenzuela, A. (1992). Changes in the xanthine dehydrogenase/xanthine oxidase ratio in the rat kidney subjected to ischemia-reperfusion stress: preventive effect of some flavonoids. *Research Communications in Chemical Pathology and Pharmacology* 78:211-218.

Sasidharan, S., Chen, Y., Saravanan, D., Sundram, K.M., and Yoga Latha, L. (2011). Extraction, isolation and characterization of bioactive compounds from plants' extracts. *African Journal of Traditional Complementary Alternative Medicine* 8:1-10.

Sauvaire, Y., Ribes, G., Baccou, J.C., and Loubatieres-Mariani, M.M. (1991). Implication of steroid saponins and sapogenins in the hypocholesterolemic effect of fenugreek. *Lipids* 26:191-197.

Schaefer, E.J., Lichtenstein, A.H., Lamon-Fava, S., McNamara, J.R., and Ordovas, J.M. (1995). Lipoproteins, nutrition, aging, and atherosclerosis. *The American Journal of Clinical Nutrition* 61:726S-740S.

Scott, R., Lintott, C., and Wilson, M. (1991). Simvastatin and side effects. *The New Zealand Medical Journal* 104:493-495.

Sen, C.K., Khanna, S., and Roy, S. (2006). Tocotrienols: vitamin E beyond tocopherols. *Life sciences* 78:2088-2098.

Sendak, R.A., Berryman, D.E. and Gellman G. (2000). Binding of hepatic lipase to heparin: Identification of specific heparin-binding residues in two distinct positive charge clusters. *Journal of Lipid Research* 41:260-268.

Serafini, M., Bugianesi, R., Maiani, G., Valtuena, S., De Santis S. and Crozier A. (2003). Plasma antioxidants from chocolate. *Nature* 424:1013.

Settasatian, N., Duong, M. and Curtiss, L.K. (2001). The mechanism of the remodeling of high density lipoproteins by phospholipid transfer protein. *Journal of Biological Chemistry* 276:26898-26905.

Shaila, H., Udupa, A., and Udupa, S. (1995). Preventive actions of *Terminalia belerica* in experimentally induced atherosclerosis. *International Journal of Cardiology* 49:101-106.

Shelness, G.S. and Sellers, J.A. (2001). Very-low-density lipoprotein assembly and secretion. *Current Opinion Lipidology* 12:151-157.

Siasos, G., Tousoulis, D., Tsigkou, V., Kokkou, E., Oikonomou, E. and Vavuranakis, M. (2013). Flavonoids in atherosclerosis: an overview of their mechanisms of action. *Current Medicinal Chemistry* 20:2641-2660.

Siefken, W., Höppner, H. and Harris, I. (2000). Regulation of cholesterol synthesis by oleic and palmitic acid in keratinocytes. *Experimental Dermatology* 9:138-145.

Skehan, P., Storeng, R., Scudiero, D., Monks, A., McMahon, J., Vistica, D. and Boyd, M.R. (1990). New colorimetric cytotoxicity assay for anticancer-drug screening. *Journal of the National Cancer Institute* 82:1107-1112.

Smith, S.S. Gropper, J.L. and Smith, J.S. (2013). Advanced nutrition and human metabolism (6th edition). Belmont, CA: Wadsworth/Cengage Learning.

Soehnlein, O. (2012). Multiple roles for neutrophils in atherosclerosis. *Circulation Research* 110:875-888.

Song, J.H., Fujimoto, K. and Miyazawa, T. (2000). Polyunsaturated (n-3) fatty acids susceptible to peroxidation are increased in plasma and tissue lipids of rats fed docosahexaenoic acid-containing oils. *Journal of Nutrition* 130:3028-3033.

Spring, M. (2009). Ethnopharmacologic analysis of medicinal plants used by Laotian Hmong refugees in Minnesota. *Journal of Ethnopharmacolology* 3:45-56.

Stamler, J., Daviglus, M.L. and Garside, D.B. (2000). Relationship of baseline serum cholesterol levels in 3 large cohorts of younger men to long-term coronary, cardiovascular, and all-cause mortality and to longevity. *JAMA: Journal of the American Medical Association* 284:311-318.

Strack, D., Vogt, T. and Schliemann, W. (2003). Recent advances in betalain research, *Phytochemistry* 62:247-269.

Sunnergren, K.P., Fairman, R.P. and Glauser, F.L. (1987). Effects of protamine, heparinase, and hyaluronidase on endothelial permeability and surface charge. *Journal of Applied Physiology* 63:112-118.

Superko, H.R., Nejedly, M. and Garrett, B (2002). Small LDL and its clinical importance as a new CAD risk factor: a female case study. *Progress in Cardiovascular Nursing* 17:167-173.

Tahanian, E., Sanchez, L.A., Shiao, T.C., Roy, R. and Annabi, B. (2011). Flavonoids targeting of IκB phosphorylation abrogates carcinogen-induced MMP-9 and COX-2 expression in human brain endothelial cells. *Drug Design, Development and Therapy* 5:299-309.

Takagi, A., Ikeda, Y., Takeda, E. and Yamamoto, A. (2000). A newly identified lipoprotein lipase (LPL) gene mutation (F270L) in a Japanese patient with familial LPL deficiency. *Biochimica et Biophysica Acta* 1502:433-434.

Talmud, P.J, Hawe, E., Miller, G.J. and Humphries, S.E. (2002). Nonfasting apolipoprotein B and triglyceride levels as a useful predictor of coronary heart disease risk in middle-aged UK men. *Arteriosclerosis, Thrombosis and Vascular Biology* 22:1918-1923.

Tan, D.T., Khor, H., Low, W., Ali, A. and Gapor, A. (1991). Effect of a palm-oil-vitamin E concentrate on the serum and lipoprotein lipids in humans. *The American Journal of Clinical Nutrition* 53:1027S-1030S.

Tangney, C.C. and Rasmussen, H.E. (2013). Polyphenols, inflammation, and cardiovascular disease. *Current Atherosclerosis Reports* 15:1-10.

Taylor, F., Huffman, M.D., Macedo, A.F., Moore, T.H., Burke, M., Davey, S.G., Ward K. and Ebrahim, S. (2013). Statins for the primary prevention of cardiovascular disease. *Cochrane Database System Revision 1*: CD004816.

Tebib, K., Besançon, P. and Rouanet, J.M. (1994). Dietary grape seed tannins affect lipoproteins, lipoprotein lipases and tissue lipids in rats fed hypercholesterolemic diets. *The Journal of Nutrition* 124:2451-2457.

Teo, S., Stirling, D., Thomas, S., Hoberman, A., Kiorpes, A. and Khetani, V. (2002). A 90-day oral gavage toxicity study of d-methylphenidate and d, l-methylphenidate in Sprague–Dawley rats. *Toxicology* 179:183-196.

Thaipong, K., Boonprakob, U., Crosby, K., Cisneros-Zevallos, L. and Hawkins, B.D (2006). Comparison of ABTS, DPPH, FRAP and ORAC assays for estimating

antioxidant activity from guava fruit extracts. *Journal of Food Composition and Analysis* 19:669-675.

Tikkanen, M.J., Wähälä, K., Ojala, S., Vihma, V. and Adlercreutz, H. (1998). Effect of soybean phytoestrogen intake on low density lipoprotein oxidation resistance. *Proceedings of the National Academy of Sciences* 95:3106-3110.

Topol, Eric. (2012). The diabetes dilemma for statin users. New York Times.

Tsai, P.J., Tsai, T.H., Yu, C.H. and Ho, S.C. (2007). Comparison of NO-scavenging and NO-suppressing activities of different herbal teas with those of green tea. *Food Chemistry* 103:181-187.

Tucker, J. and Townsend, D. (2005). Alpha-tocopherol: roles in prevention and therapy of human disease. *Biomedicine and Pharmacotherapy* 59:380-387.

van Heck, M., Farley, C. and Compton D.S. (2003). Ezetimibe inhibits cholesterol absorption but does not affect acute hepatic or intestinal cholesterol synthesis in rats. *British Journal of Pharmacolology* 138:1459-1464.

Vance, J.E. and Vance, D.E. (2002). Biochemistry of lipids, lipoproteins and membranes. Amsterdam, Elsevier.

Ververidis, F., Trantas, E., Douglas, C., Vollmer, G., Kretzschmar, G. and Panopoulos, N.(2007). Biotechnology of flavonoids and other phenylpropanoid-derived natural products. Part I: Chemical diversity, impacts on plant biology and human health. *Biotechnology Journal* 2:1214-1234.

Velioglu, Y., Mazza, G., Gao, L. and Oomah, B. (2010) Antioxidant activity and total phenolics in selected fruits, vegetables and grain products. *Journal of Agricultural Food Chemistry* 46:4113-4117.

Velioglu, Y., Mazza, G., Gao, L., and Oomah, B. (1998). Antioxidant activity and total phenolics in selected fruits, vegetables, and grain products. *Journal of Agricultural and Food Chemistry* 46:4113-4117.

Venkatalakshmi, P. and Senthamaraiselvi, V. (2012). Anti ulcer effect of *Basella alba* leaf extract in aspirin induced albino rats. *International Journal of Pharmaceutical Sciences and Research* 3:2539-2542.

Vimala, S., Rohana, S., Rashih, A. and Juliza, M. (2012). Antioxidant evaluation in Malaysian medicinal plant: *Persicaria minor* (Huds.) leaf. *Science Journal of Medicine and Clinical Trials* 34:123-135.

Vinson, J.A., Dabbagh, Y.A., Serry, M.M. and Jang, J. (1995). Plant flavonoids, especially tea flavonols, are powerful antioxidants using an *in vitro* oxidation model for heart disease. *Journal of Agricultural and Food Chemistry* 43:2800-2802.

Vinson, J.A. and Jang, J. (2001). *In vitro* and *in vivo* lipoprotein antioxidant effect of a citrus extract and ascorbic acid on normal and hypercholesterolemic human subjects. *Journal of Medicinal Food* 4:187-192.

Vita, J.A. (2005). Polyphenols and cardiovascular disease: Effects on endothelial and platelet function. *The American Journal of Clinical Nutrition* 81:292S-297S.

Vogel, R.A. (1997). Coronary risk factors, endothelial function, and atherosclerosis: a review. *Clinical Cardiology* 20:426-432.

Walker, C. and Reamy, B.V. (2009). Diets for cardiovascular disease prevention: What is the evidence? *American Family Physician* 79:571-578.

Wang, H. and Helliwell, K. (2001). Determination of flavonols in green and black tea leaves and green tea infusions by high-performance liquid chromatography. *Food Research International* 34:223-227.

Wang, J., Zhou, G., Chen, C., Yu, H., Wang, T., Ma, Y. and Sun, J. (2007). Acute toxicity and biodistribution of different sized titanium dioxide particles in mice after oral administration. *Toxicology Letters* 168:176-185.

Wang, N., Silver D.L. and Costet, P. (2000). Specific binding of ApoA1, enhanced cholesterol efflux and altered plasma membrane morphology in cells expressing ABCA1. *Journal of Biological Chemistry* 275:33053-33058.

Wang, Z., Huang, Y., Zou, J., Cao, K., Xu, Y. and Wu, J.M. (2002). Effects of red wine and wine polyphenol resveratrol on platelet aggregation *in vivo* and *in vitro*. *International Journal of Molecular Medicine* 9:77-80.

Waqar, A.B., Koike, T., Yu, Y., Inoue, T., Aoki, T., Liu, E. and Fan, J. (2010). High-fat diet without excess calories induces metabolic disorders and enhances atherosclerosis in rabbits. *Atherosclerosis* 213:148-155.

Wassmann, S., Laufs, U. and Baumer, A.T. (2009). HMG-CoA reductase inhibitors improve endothelial dysfunction in normocholesterolemic hypertension via reduced production of reactive oxygen species. *Hypertension* 37:1450-1457.

Whiting, B.M., Anderson, J.L. and Muhlestein, J.B. (2005). Candidate gene susceptibility variants predict intermediate end points but not angiographic coronary artery disease. *American Heart Journal* 150:243-250.

Williams, D. and Feely, J. (2002). Pharmacokinetic-pharmacodynamic drug interactions with HMG-CoA reductase inhibitors. *Clinical Pharmacokinetics* 41:343-370.

Wong, H. and Schotz, M.C. (2002).The lipase gene family. *Journal of Lipid Research* 43:993-999.

Wong, J., Quinn, C. and Brown, A. (2006). SREBP-2 positively regulates transcription of the cholesterol efflux gene, ABCA1, by generating oxysterol ligands for LXR. *Biochemistry Journal* 400:485-491.

Wu, K., Bowman, R. and Welch, A.A. (2007). Apolipoprotein E polymorphisms, dietary fat and fibre, and serum lipids: the EPIC Norfolk study. *Europen Heart Journal* 28:2930-2936.

Yahaya, Y.A. and Don, M.M. (2012). Evaluation of *Trametes lactinea* extracts on the inhibition of hyaluronidase, lipoxygenase and xanthine oxidase activities *in vitro*. *Journal of Physical Science* 23:1-15.

Yamamoto, S. (1992). Mammalian lipoxygenases: molecular structures and functions. *Biochimica et Biophysica Acta (BBA)- Lipids and Lipid Metabolism* 1128:117-131.

Yamamoto, Y. and Gaynor, R.B. (2001). Therapeutic potential of inhibition of the NF-κB pathway in the treatment of inflammation and cancer. *Journal of Clinical Investigation* 107:135-142.

Yancey, P.G., Kawashiri, M.A. and Moore, R. (2004). *In vivo* modulation of HDL phospholipid has opposing effects on SR-BI- and ABCA1-mediated cholesterol efflux. *Journal of Lipid Research* 45:337-346.

Yang, J., Goldstein, J.L. and Hammer, R.E. (2001). Decreased lipid synthesis in livers of mice with disrupted Site-1 protease gene. *Proceedings of the National Academy of Sciences* USA 98:13607-13612.

Yang, R.Y., Lin, S. and Kuo, G. (2008). Content and distribution of flavonoids among 91 edible plant species. *Asia Pacific Journal Clinical Nutrition* 17:275-279.

Yang T., Espenshade, P.J. and Wright, M.E. (2002). Crucial steps in cholesterol homeostasis: Sterols promote binding of SCAP to INSIG-1, a membrane protein that facilitates retention of SREBPs in ER. *Cell* 110:489-500.

Yao, L., Heubi, J.E. and Buckley, D.D. (2002). Separation of micelles and vesicles within luminal aspirates from healthy humans: solubilization of cholesterol after a meal. *Journal of Lipid Research* 43:654-660.

Yasmin, H., Kaisar, M.A., Sarker, M.M.R., Rahman, M.S. and Rashid, M.A. (2009). Preliminary anti-bacterial activity of some indigenous plants of Bangladesh. *Dhaka Univiversity Journal of Pharmacological Sciences* 8:61-65.

Yeap, S.K. (2014). *In vivo* antioxidant and hypolipidemic effects of fermented mung bean on hypercholesterolemic mice. *Evidence-Based Complementary and Alternative Medicine* 508029.

Yen, G.C. and Chen, H.Y. (1995). Antioxidant activity of various tea extracts in relation to their antimutagenicity. *Journal of Agricultural and Food Chemistry* 43:27-32.

Yokozawa, T., Cho, E.J., Sasaki, S., Satoh, A., Okamoto, T. and Sei, Y. (2006). The protective role of Chinese prescription *Kangen-karyu* extract on diet-induced hypercholesterolemia in rats. *Biological and Pharmaceutical Bulletin* 29:760-765.

Yusuf, S., Reddy, S. and Ounpuu, S. (2001). Global burden of cardiovascular diseases part I: general considerations, the epidemiologic transition, risk factors, and impact of urbanization. *Circulation* 104:2746-2753.

Zamora-Ros, R., Agudo, A., Luján-Barroso, L., Romieu, I., Ferrar,i P. and Knaze, V. (2012). Dietary flavonoid and lignan intake and gastric adenocarcinoma risk in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. *American Journal of Clinical Nutrition* 96:1398-1408.

Zhang, D.W., Lagace, T.A. and Garuti, R. (2007a). Binding of proprotein convertase subtilisin/kexin type 9 to epidermal growth factor-like repeat A of low density lipoprotein receptor decreases receptor recycling and increases degradation. *Journal Biological Chemistry* 282:18602-18612.

Zhang, H.W., Zhang, Y.H., Lu, M.J., Tong, W.J. and Cao, G.W. (2007b). Comparison of hypertension, dyslipidaemia and hyperglycaemia between buckwheat seed-consuming and non-consuming Mongolian-Chinese populations in Inner Mongolia, China. *Clinical and Experimental Pharmacology and Physiology* 34, 838-844.

Zhang, N., Huang, C. and Ou, S. (2011). *In vitro* binding capacities of three dietary fibers and their mixture for four toxic elements, cholesterol, and bile acid. *Journal of Hazardous Materials* 186:236-239.

Zhang, Y., Li, L., You, J., Cao, J. and Fu, X. (2013). Effect of 7-Difluoromethyl-5, 4′-dimethoxygenistein on aorta atherosclerosis in hyperlipidemia ApoE mice induced by a cholesterol-rich diet. *Drug Design, Development and Therapy*, 7: 233-242.

Zhang, W., Iso, H., Ohira, T., Date, C., Tamakoshi, A. and JACC Study Group. (2012). Associations of dietary magnesium intake with mortality from cardiovascular disease: the JACC study. *Atherosclerosis* 221:587-595.

LIST OF PUBLICATIONS

Baskaran Gunasekaran, Shamala Salvamani, Noor Azmi Shaharuddin, Siti Aqlima Ahmad , Mohd Yunus Shukor (2014). Anti-atherosclerotic effects of plant flavonoids, *BioMed Research International Journal*, 480258. (IF: 2.88, Q2)

Baskaran, Gunasekaran, Shamala Salvamani, Siti Aqlima Ahmad, Noor Azmi Shaharuddin, Parveen Devi Pattiram, and Mohd Yunus Shukor (2015). HMG-CoA reductase inhibitory activity and phytocomponent investigation of *Basella alba* leaf extract as a treatment for hypercholesterolemia. *Drug Design, Development and Therapy* 9:509-517. (IF: 3.026, Q2)

Baskaran Gunasekaran, Shamala Salvamani, Siti Aqlima Ahmad and Mohd Yunus Shukor (2014). Evaluation of acute and subchronic toxicity of *Basella alba* leaf extract in rats and cytotoxic potential *in vitro*. *Drug Design, Development and Therapy* (Accepted) (IF: 3.026, Q2)

Baskaran, Gunasekaran, Shamala Salvamani, Siti Aqlima Ahmad, Mohd Khalizan Hasbullah and Mohd Yunus Shukor (2015). Antioxidant, anti-inflammatory and properties analysis of *Basella alba* leaf extract (Submitted to BioMed Research International).

Baskaran, Gunasekaran, Shamala Salvamani, Azrina Azlan, Siti Aqlima Ahmad, Swee Keong Yeap and Mohd Yunus Shukor (2015). Hypocholesterolemic and antioxidant effects of *Basella alba* inhibit atherosclerosis in hypercholesterolemia-induced rabbits. .*Evidence-Based Complementary & Alternative Medicine*. (Accepted) (IF: 1.88, Q2)

Baskaran Gunasekaran, Noor Azmi Shaharuddin, Azrina Azlan and Mohd Yunus Shukor (2013). The inhibitory effect of some Malaysian plant extracts on the 3-hydroxy-3-methyl glutaryl coenzyme A reductase, 38th Annual Conference of Malaysian Society for Biochemistry & Molecular Biology.

Baskaran Gunasekaran, Noor Azmi Shaharuddin, Azrina Azlan and Mohd Yunus Shukor (2014). Anti cholesterolemic effects of *Basella alba* inhibits atherosclerosis in hypercholesterolemia-induced rabbits, Monash University Science Symposium.

Baskaran, Gunasekaran, Shamala Salvamani, Siti Aqlima Ahmad, Noor Azmi Shaharuddin, Parveen Devi Pattiram, and Mohd Yunus Shukor (2015). HMG-CoA reductase inhibitory activity and phytocomponent investigation of *Basella alba* leaf extract as a treatment for hypercholesterolemia, International Conference on Science, Technology, Engineering and Management, Jeppiar Engineering College, Chennai, India.

PATENT

Mohd Yunus Shukor, **Baskaran Gunasekaran**, Shamala Salvamani, Azrina Azlan, Md Zuki Abu Bakar and Siti Aqlima Ahmad. Novel compound for use as medicament for treatment of hypercholesterolemia and atherosclerosis (Patent file-PI 2014704025).

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