UNIVERSITI PUTRA MALAYSIA

EFFECTIVENESS OF EPA+DHA FROM YELLOW STRIPE SCAD FISH ON LIPID PROFILE, PLATELET AND ENDOTHELIAL-RELATED ACTIVATION BIOMARKERS AMONG OVERWEIGHT ADULTS

YAKUBU ABDULRAHMAN

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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

November 2020

DEDICATION

This research work is dedicated with all humanity and respect to my beloved parent and wife for their love, guidance, support and patience.

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

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Chairman : Associate Professor Sabariah Md Noor, MD, MPath
Faculty : Medicine and Health Sciences

Overweight is a global health condition that can lead to cardiovascular diseases (CVDs). Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) from salmon have beneficial effects on CVDs, while local yellow stripe scad (YSS), has been described as having same. However, the beneficial effects of EPA+DHA still remain ambiguous. The present study investigated the impact of 900mg EPA+DHA intake from YSS and salmon on parameters including body mass index (BMI), serum leptin, lipid profile and blood pressure (atherosclerosis marker), platelet activation markers (thrombotic makers), platelet and endothelial inflammation markers as (CVD markers) and protein expression level of NF-kB and PPAR-γ (as therapeutic markers) on healthy overweight subjects. For 60 days, equally randomized subjects received either 269g of YSS whole fish per day, to obtain 2,103mg of EPA+DHA per day for three days in a week that provides 6,310 mg of EPA+DHA (approximately 900mg/day) or 217g of salmon fish fillet per day that provides 2,103mg of EPA+DHA per day for three days and contained 6,310 mg of EPA+DHA/week (approximately 900mg/day).The primary and secondary results were recorded and data were analyzed quantitatively and qualitatively by a two-tailed paired Student's T-test and Analysis of Covariance (ANCOVA) respectively. Significant differences were observed in serum leptin for both YSS (+2.0 ng/ml) and salmon (+1.9 ng/ml). Increased significant differences were observed in HDL-C (+0.0711mmol/L) and LDL-C (+0.171mmol/L) in YSS-baseline but not in VLDL-cholesterol (+0.02mmol/L). Significant differences were also observed in VLDL (+0.049 mmol/L) and HDL-C (+0.06 mmol/L) in salmon-baseline but not in LDL-C. Non-significant differences were also observed in body mass index (BMI) (+0.05kg/m2), leptin (+0.541ng/ml), HDL-C (+0.008mmol/L), LDL-C (+0.015mmol/L), and VLDL-C (+0.03mmol/L) in YSS and salmon, as independent variables including the effects of time and interactions. No significant difference ($p>0.05$) was observed for PMP-CD62 (+222.6 PMPs/µl), PMP-CD41 (316.3

PMPs/µl), and PMP-PS-Annexin-5 (237.5 PMPs/µl) as independent variables for YSS and salmon including the effects of time and interactions. No significant difference was also observed in vWF (+11.2pg/ml), MCP-I (+0.5pg/ml), P-selectin (+20.5pg/ml), sCD40L (+0.3pg/ml), IL-1β (+0.378pg/ml) and TNF-α (+1.3pg/ml) including the effects of time and interactions in YSS and salmon as independent variables. The study observed no significant difference in NF-kB, (3.9 ng/ml) in YSS-salmon and PPAR-γ (+3.7ng/ml) in YSS-salmon as independent variable. The inferential statistic, "ANCOVA" showed that YSS and salmon treatments as an independent variable was not significant in BMI, serum leptin, lipid profile, blood pressure as (atherosclerotic makers) and platelet activation markers as (thrombotic makers), platelet and endothelial inflammation markers as (CVD markers) and protein expression level of NF-kB and PPAR-γ as (therapeutic markers). Qualitative data analysis showed that both primary and secondary data, were similar in performance. The study shows positive effects of EPA+DHA treatments from salmon and from YSS. The study upheld the (Ho) null hypothesis in which the effect of EPA+DHA from salmon on atherosclerosis, thrombosis, and CVD related parameters did not change and was no different from EPA+DHA in YSS including the effects of time and interactions. In future intervention investigations on EPA+DHA, cellular phospholipid membrane content, a controlled randomized study, is vital to further validate the similarity effects of EPA+DHA from both YSS and salmon intake.

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

KEBERKESANAN EPA+DHA IKAN SELAR KUNING KE ATAS PROFIL LIPID, PLATELET DAN BIOPENANDA PENGAKTIFAN BERKAITAN ENDOTELIAL DALAM KALANGAN ORANG DEWASA BERAT BERLEBIHAN

Oleh

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Berat berlebihan merupakan kondisi kesihatan global yang membawa kepada penyakit kardiovaskular (CVD). Asid Eikosapentaenoik (EPA) dan asid dokosaheksaenoik (DHA) ikan salmon mempunyai kesan yang bermanfaat ke atas CVD, manakala ikan selar kuning (YSS), diperkatakan sebagai mempunyai kesan yang sama. Walau bagaimanapun, kesan bermanfaat EPA+DHA masih lagi kurang jelas. Kajian ini menyelidiki impak 900mg EPA+DHA/hari bagi tujuh hari pengambilan YSS dan salmon ke atas parameter termasuk indeks jisim tubuh (BMI), leptin serum, profil lipid dan tekanan darah (penanda aterosklerosis), penanda pengaktifan platelet (penanda trombotik), platelet dan penanda inflamasi endotelial (penanda CVD) dan tahap ekspresi protein NF-kB dan PPAR-γ (sebagai penanda terapeutik) ke atas subjek berat berlebihan sihat. Selama 60 hari, subjek dirawatkan secara sama rata menerima sama ada 269g seluruh ikan YSS per hari, bagi mendapatkan 2,103mg EPA+DHA per hari untuk 3 hari setiap minggu yang memberikan 6,310 mg EPA+ DHA (anggaran 900mg/hari) atau 217g filet ikan salmon per hari yang memberikan 2,103mg EPA+DHA per hari untuk 3 hari dan mengandungi 6,310mg EPA+DHA/minggu (anggaran 900mg/hari) dalam dua fasa kajian. Pengambilan ikan telah ditukar selepas 60 hari tempoh pengosongan. Dapatan primer dan sekunder telah direkodkan dan data telah dianalisis secara kuantitatif dan kualitatif masing-masing melalui ujian T Pelajar berpasangan dua hujung dan Analisis Kovarians (ANCOVA). Perbezaan yang signifikan telah dikesan dalam leptin serum bagi kedua-dua YSS (+2.0 ng/ml) dan salmon (+1.9 ng/ml). Perbezaan signifikan yang dipertingkatkan telah dikesan dalam HDL-C (+0.0711mmol/L) dan LDL-C (+0.171mmol/L) dalam garis asas YSS tetapi bukan dalam VLDL-kolesterol (+0.02mmol/L). Perbezaan yang signifikan juga telah dikesan dalam VLDL (+0.049 mmol/L) dan HDL-C (+0.06 mmol/L) dalam garis asas salmon tetapi bukan dalam LDL-C. Perbezaan yang tak signifikan juga telah

dikesan dalam indeks jisim tubuh (BMI) (+0.05kg/m2), leptin (+0.541ng/ml), HDL-C (+0.008mmol/L), LDL-C (+0.015mmol/L), dan VLDL-C (+0.03mmol/L) dalam YSS dan salmon, sebagai pemboleh ubah tak bersandar termasuk kesan masa dan interaksi. Perbezaan yang tidak signifikan ($p>0.05$) telah dikesan bagi PMP-CD62 (+222.6 PMPs/µl), PMP-CD41 (316.3 PMPs/µl), dan PMP-PS-Annexin-5 (237.5 PMPs/µl) sebagai pemboleh ubah tak bersandar bagi YSS dan salmon termasuk kesan masa dan interaksi. Perbezaan yang tidak signifikan juga telah dikesan dalam vWF (+11.2pg/ml), MCP-I (+0.5pg/ml), P-selektin (+20.5pg/ml), sCD40L (+0.3pg/ml), IL-1β (+0.378pg/ml) dan TNF-α (+1.3pg/ml) termasuk kesan masa dan interaksi dalam YSS dan salmon sebagai pemboleh ubah tak bersandar. Kajian mendapati tiada perbezaan yang signifikan dalam NF-kB, (3.9 ng/ml) dalam YSS-salmon dan PPAR-γ (+3.7ng/ml) dalam YSS-salmon sebagai pembolehubah tak bersandar. Statistik inferensi, "ANCOVA" menunjukkan bahawa rawatan YSS dan salmon sebagai pemboleh ubah tak bersandar adalah tidak signifikan dalam BMI, leptin serum, profil lipid, tekanan darah sebagai (penanda aterosklerotik) dan penanda pengaktifan platelet sebagai (penanda trombotik), platelet dan penanda inflamasi endotelial sebagai (penanda CVD) dan tahap ekspresi protein bagi NF-kB dan PPAR-γ sebagai (penanda terapeutik). Analisis data kualitatif menunjukkan bahawa kedua-dua data primer dan sekunder, adalah sama dari segi prestasi. Kajian ini menunjukkan kesan positif rawatan EPA+DHA daripada salmon dan daripada YSS. Kajian ini mengesahkan hipotesis null (Ho), iaitu kesan EPA+DHA salmon ke atas aterosklerosis, trombosis, dan parameter berkaitan CVD tidak berubah dan adalah tidak berbeza daripada EPA+DHA dalam YSS termasuk kesan masa dan interaksi. Bagi penyelidikan intervensi masa hadapan ke atas EPA+DHA, kandungan membran fosfolipid selular, suatu kajian terawak terkawal, seterusnya adalah amat perlu bagi mengesahkan kesan kesamaan EPA+DHA daripada kedua-dua pengambilan YSS dan salmon.

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This thesis was submitted to the Senate of the 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

AA	Arachidonic acid
ADP	Adenosine diphosphate
AHA	American Heart Association
ALA	Alpha linoleic acid
ANOVA	Analysis of variance
ANCOVA	Co-variance of ANOVA
BP	Blood pressure
BMI	Body mass index
CAD	coronary artery disease
CD41	Platelet microparticle marker
CD41/CD61	Integrin glycoprotein (GP) IIb/IIIa
CD42	GpIb, GPIb-V-IX,
CD62P	P-selectin
CD62E	E-selectin
sCD40L	Soluble CD40 Ligand
CHD	Coronary heart disease
CVDs	Cardiovascular disorders
CXC	Chemokine
CXCR4	CD184 chemokine
CCL5	RANTES
DAG	1,2-diacylglycerol
DHA	Docosahexaenoic acid
ECs	Endothelial cells
ELISA	Enzyme-Linked Immunosorbent Assays

EPA	Eicosapentaenoic Acid
ENA-78-	Epithelial neutrophil-activating protein 78
HDL-C	High-Density Lipoprotein Cholesterol
ICAM-1	Intercellular Adhesion Molecule-1
IP3	Inositol 1,4, 5 triphosphates
IL-1 β	Interleukin-1 β
IL-6	Interleukin-6
LDL-C	Low-density lipoprotein (LDL) cholesterol
MCP-1	Monocyte Chemoattractant Protein-1
MMPs	Matrix metallopeptidases
NO	Nitric Oxide
PF-4	platelet factor 4
PLC	PLC - Phospholipase C
STEM	Segment Elevation Myocardial Infarction
TC	Total cholesterol
TG	Triglycerides
TGF-β	Transforming growth factor-beta
TNF-α	Tumor Necrosis Factor-alpha
TXA2	Thromboxane-A2
OB-Gene	Obesity gene
ObRb	Leptin receptor
PAI-1	Plasminogen Activator Inhibitor,
PAR-1	Protease-Activated Receptors-1
PI3	Phosphatidylinositol3-kinase
PMPs	Platelet Micro-Particles
PDGF	Platelet-derived growth factor

PECAM	Platelet Endothelium Adhesion Molecule-1(CD31)
RANTES	Regulated on Activation Normal T-cell Expressed and Secreted
ROS	Reactive Oxygen Species
NSTEM	Non-Segment Elevation Myocardial Infarction
VCAM-1	Vascular Cell Adhesion Molecules-1
VSMC-1	Vascular Smooth Muscle Cells
WHO	World health organization
YSS	Yellow Stripe Scad

CHAPTER 1

INTRODUCTION

1.1 Background of the study

Overweight and obesity are two major risk factors that contribute to global health burden which impair quality of life, raising cost of health care and budget. They predispose an individual to multiple inflammatory health issues such as non-communicable disease (NCD) like atherosclerosis, type II diabetes, cancers, thrombosis and cardiovascular disease (CVD) worldwide (Csige et al., 2018; Templin et al., 2019). Global overweight and obesity cases have increased three-fold since 1980. According to World Health Organisation (WHO). in 2016, approximately 1.9 billion adult population of 18 years old or more were overweight and more than 650 million were obese worldwide which represented about 39 % and 13 % of overweight and obese adults respectively (WHO, 2016).

In 2017, in the Southeast Asian region, Malaysia had the highest overweight prevalence with approximately 39 %, followed by Singapore (37 %) (Tim-Niklas, 2017). Malaysia was facing an overweight and obesity pandemic, with over half of the country's population was either overweight or obese when compared to the last 20 year, by which only 4 % of the population was considered overweight or obese (Tim-Niklas, 2017). The data were supported by the National Health and Morbidity Survey 2019 (NHMS, 2019) which presented that 50.1% Malaysian were overweight or obese indicating that overweight/obese had reached a pandemic level with CVD as the leading cause of death (Ahmad et al., 2018). Currently, CVD is the major cause of death globally, where out of 57 million deaths recorded in 2018, NCDs accounted for 71% of which 31% were from CVD, the highest cause of death (WHO, 2018). The Malaysia's Ministry of Health reported that in 2016, CVDs were tagged as among the ten major causes of death in both private and government hospitals stood at 27.7% (Ahmad et al., 2018). A report from WHO indicated that 76% of death came from NCDs, and 35% from CVDs, the highest on record (WHO, 2018). Against this background, comprehensive management and urgent control of the epidemic growth of overweight and obesity in the country is imperative to address the matter in hand.

Literature have shown that excessive adipose tissue induces metabolic abnormality via receptor signalling, which puts an individual at risk of dyslipidaemia, an elevation of plasma cholesterol, triglycerides (TGs), or both, or a low high-density lipoprotein cholesterol (HDL-C) level that contributes to the development of atherosclerosis. For example, it is known that overweight condition induces reduced HDL-C, increased low-density lipoprotein cholesterol (LDL-C), increased very low-density lipoprotein cholesterol (VLDL-C), increased triglycerides (TG), increased total cholesterol (TC), hypertension, leptin resistance, and increased oxidized low-density lipoprotein cholesterols (ox-LDL-C) although, both LDL and VLDL are regarded as harmful cholesterols (Kaess et al., 2014). Several findings

have shown that atherosclerosis is an inflammatory disease. It has been documented that it involved multiple immune cells, with platelet and ox-LDL as initiator, recruitment, and migration of monocyte and neutrophils into the subendothelial space leading to thrombotic complication (Lebas et al., 2019; Nording et al., 2015; Frostegard, 2013). Leptin resistance and ox-LDL-C have their receptors in platelets. They have been reported to activate platelets via independent pathological pathways, one of the links connecting overweight or obesity conditions and CVD (Obermayer et al., 2018). In the present study, platelet was chosen as a point of focus, due to its multiple receptors and focal adhesion to different immune cells (Rivera et al., 2009; Saboor et al., 2013).

Literature have it that platelet is a complex multifactorial cell, with multiple glycoproteins as a receptor that interacts and activates most inflammatory cells to produce tissue factor (TF) such as endothelial cells, neutrophil, monocytes, and vascular smooth muscles cell (VSMC) which have been documented to be the major cells involved in atherosclerosis and CVD (Badimon et al., 2012). Platelet is known to be the only cell type that can form thrombosis due to the presence of GPIIα/IIIβ receptors. Thus, activated platelet releases both platelet microparticle (PMPs) and platelet inflammation and activation markers. PMPs are small particles ranging from (0.1–1 μm) in diameter. They are microvesicles generally released during platelet activation or apoptosis, which is 50-100 % more thrombotic than the platelet itself (Sinauridze et al., 2007). Platelets microparticles are the most abundant microparticles in human blood accounting for approximately 70–90% of all circulating microparticle (Alarcon, 2019; Berckmans et al., 2001). PMPs are also distinguished by phospholipid asymmetry disturbance, which results in calcium-dependent phosphatidylserine (PS) exposure on outer leaflet. Exposed PS, therefore, binds with ECs tissue factor (TF) to initiate extrinsic coagulation pathways which forms the basis of thrombosis (Grande et al., 2019; Lukasik et al., 2012).

Rayes et al., (2019) published that activated platelets also released cytokines and chemokines and increased the permeability of damaged arterial wall. This activated vascular endothelium (ECs), recruited monocytes, and neutrophil via platelet complex interaction with P-selectin and Rantes. Subsequently, recruited monocytes differentiated into macrophages in the presence of platelet factor 4 (PF4) that engulfed lipid (LDL-C, VLDL-C, and TG) via the scavenger receptor to form a lipid-laden foam cell, called fatty streaks known as atherogenic. Atherogenesis mediated the migration of vascular smooth muscle cells (VSMC) from media to intima, with subsequent deposition and proliferation of extracellular matrix (ECM) to form mature plaque characterized by a fibrous cap as protection. Exposure of fibrous cap during apoptosis or acute rupture, reacted with phosphatidylserine (PS) from activated platelet and tissue factor (TF) from both neutrophil and monocytes leading to complex activation of a coagulation factor. This was the basis of thrombosis that formed the acute complication, observed in CVD (Freemark, 2019; Lisman, 2018; Riyahi et al., 2018; Sprague and Khalil, 2009).

It is known that some of these chemokines and cytokines from activated platelets affected a wide variety of biological functions, signaling via a transcription factor called Nuclear factor kappa-activated B-cells (NF-κB) found in the nucleus of endothelial cells (ECs), VSMC, neutrophil and monocytic cells (Kojok et al., 2019; Liu et al., 2017; Lindmar et al., 2000; Stokes and Granger, 2012). Studies have indicated that NF-κB regulates several inflammatory genes that play a crucial role in the pathogenesis of atherosclerosis and CVD. NF-κB is also a possible therapeutic target for thrombosis and atherosclerotic events (Fiordelisi et al., 2019). The NF-κB family is made of five related structures, including NF-κB1, NF-κB2, RelA, RelB, and c-Rel. The NF-κB pathway is said to be stimulated by cytokine and stress to activate IKK. Activated IKK subsequently phosphorylates IκBα to trigger the degradation of IκBα, resulting in translocation of NF-κB1 into the nucleus of target cells (Hayden and Ghosh, 2008; Zhang and sun, 2015). Surprisingly, dysregulation of NF-κB activation is a hallmark of inflammatory diseases. Fiordelisi et al., (2019) cited that the therapeutic target of NF-KB for the treatment of inflammatory diseases required a better understanding of the mechanism underlying NF-kB activation and pro-inflammatory activity.

Studies on both human and animals by Innes and Calder, (2018); Calvo et al., (2017) and Desnoyers, (2018) have demonstrated that eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) from fatty fish such as salmon, have shown its cardioprotective capabilities via harmonization of phospholipid membrane to modified cellular receptors, modulates cardiac ion channels, and cardiac arrhythmias, reduces cellular activation, decreases cholesterol level, modulates platelets activation and aggregation, reduces chronic inflammation, decreases thrombosis and CVD. Effects of EPA+DHA have been established to be time-dependent i.e. the longer the time of intake of EPA+DHA, the more, effective it becomes (Allam-Ndoul et al., 2017; Teague et al., 2014). In fact, intakes of EPA+DHA from fish have not established of its interaction effect with other drugs or platelet coagulation factor to cause bleeding, that is, interact with antiplatelet drugs such as clopidogrel, aspirin, and glycoprotein IIb/IIIa receptor antagonists, including all anticoagulants such as warfarin, and heparin. No studies have indicated that EPA+DHA caused bleeding episodes (Mori et al., 1997; Pryce et al., 2016). Zibaeenezhad et al., (2017) reported that intake of fresh fish fillet was significantly better in modifying lipid profiles than an omega-3 supplement or fish oil., In spite of this, there have been no report describing any effect of EPA+DHA from fish on platelet-related biomarkers (Kander et al., 2018; Poreba et al., 2017; Thornton, 2018).

Aside from marine source, EPA+DHA are also produced by plants such as from canola, walnut, and flax. It is called alpha-linolenic acid (ALA), which is also a dietary supplement. Similarities between plant and marine sources of EPA+DHA are still not clear. Mendoza-Núñez et al., (2019) have demonstrated a number of ALA health benefits. Isaksen et al., (2018) reported that intake of EPA+DHA from fish significantly lowered the risk of venous thromboembolism. They compared study participants consuming more than 2.64 servings per day of total fish to those with an intake of fewer than 0.42 servings per day.

Peroxisome proliferator-activated receptor (PPAR-γ), is a transcription factor, which regulates enzymes needed for glucose and fatty acid metabolism (Ahmadian et al., 2013). PPAR-γ is a therapeutic target of many pharmaceutical companies to modulate many biological functions, such as metabolic syndrome, insulin resistance, leptin resistance, excessive glucose, and cholesterol via activation TCA-cycle (Hans et al., 2017). Remarkably, EPA+DHA is one of the ligands that activates PPARγ activity in promoting fat and glucose metabolism (Grygiel-Górniak 2014; Janani and Kumari, 2014).

1.2 Statement of the problem

Being overweight or obese can greatly increase the risk of other health problems particularly CVD. Overweight and obesity are characterized by increased LDL-C level and leptin resistance that predispose an individual to high cholesterol level, platelets and endothelial cell activation along with dysregulation of NF-kB with a resulting consequence of cardiovascular event. Recent data showed that Malaysia has been tagged with the highest overweight prevalence in Southeast Asia. CVDs death has been recorded to be the highest among ten different major causes of death (Ahmad et al., 2018). Treatments of CVD, have been a big financial burden to both government and private's individual. Some intervention studies have evaluated the effect of fish intake on CVD and its risk marker. Unfortunately, they are limited studies on crossover trials conducted on healthy overweight subject. Yellow stripe scads (YSS) is a local Malaysian marine fish, frequently consumed, which is cheap and affordable (Ahmad et al., 2016). Some researchers have reported that YSS has a good quality DHA that is comparable to wild salmon (Abd Aziz et al., 2013). However, the effects of EPA+DHA from YSS on overweight and cardiovascular risk markers is still lacking. Against this background, the present study was conducted to explore the effects of EPA+DHA from both YSS and salmon on CVD related risk markers as cardioprotective via fish consumption. It would be a very meaningful investigation should both fish species have similar EPA+DHA.

1.3 Justification for the study

A number of studies have highlighted the dietary role of fatty fish as an important source for EPA+DHA from varieties of fish such as mackerel, herring, tuna, cod, and salmon. These fatty and lean fish provide daily EPA+DHA ranging from 700-1200 mg/100 g of wet fish fillet (Rincón-Cervera et al., 2020; Gammone et al., 2018; Greene et al., 2013; Zygmunt and Joanna, 2012; Soltan and Gibson, 2008). High-fat content of salmon fish fillet contributes 1200-800 mg of EPA+DHA/100 g of fish fillet (Kitson et al., 2009). In the present study, platelets were chosen as target cells due to their multiple receptors, which interact and activate other cells such as endothelial cells, monocytes, and neutrophils to bring about thrombosis. Platelets are the only cells that can form thrombosis due to the presence of GPIIb/IIIa receptors. However, knowledge of EPA+DHA from YSS on cardiovascular protection is limited. Previous studies have identified three types of local fish that could supply the daily needs of EPA+ DHA, as well as macro- and

micronutrients (Nurnadia et al., 2013). These fish types include Japanese threadfin bream (kerisi), Fringescale sardinella (tamban) and Yellow stripe scad (YSS) (or selar kuning). These fish types provide 436 mg, 551 mg, and 879 mg of EPA+DHA/100 g wet fish fillet, respectively. Among the three, YSS contains the highest EPA+DHA with good nutritional value (Abd Aziz et al., 2013). According to Hamilton et al., (2005), EPA content of wild salmon is 414 mg/100g as compared to EPA content farmed salmon (1079 mg/100 g), supermarket salmon (969 mg/100 g). Local Malaysian fish such as Hardtail scad, Indian mackerel, and Malabar red snappers, has lower content of EPA+DHA (2.7–343.0 mg/100 g). Abd Aziz et al., 2013) compared DHA content of wild salmon (629 mg/100 g) and farmed salmon (2633 mg/100 g) with local Malaysian fish (9.0–277.1 mg/100 g). With the exception of YSS, local–Malaysian fish contains slightly higher DHA content (782.1 mg/100 g) (Abd Aziz et al., 2013) than wild salmon (629 mg/100 g) (Hamilton et al., 2005). Several other studies have also shown the effects of EPA+DHA from fish oil and fish fillet on platelet activation markers, inflammation markers, and platelet phospholipids membrane reduces thrombosis markers and coronary heart diseases (Adili et al., 2018; Dinicolantonio, 2019). The effects of EPA+DHA from YSS on platelets, thrombosis, and CVD outcomes are not clear and not well-understood. Therefore, the primary aim of the present study was to compare the effects 900mg of EPA+DHA intake per day from YSS and salmon on primary and secondary out comes from overweight healthy subject.

1.4 General objective

To investigate the effects of EPA+DHA, time, and interaction from YSS in comparison to salmon fish fillet on atherosclerosis, thrombotic cardiovascular, and target therapeutic markers, among healthy overweight adult subjects.

1.4.1 Specific objectives

i. To determine and compare means between before and after treatments of EPA+DHA from YSS and salmon for 60 days on atherosclerosis markers: (BMI, lood pressure, platelet count, and lipid profile [LDL-C, TC, TG, HDL-C, and VLDL]);
ii. To determine and compare means between before and after treatment of EPA+DHA from YSS and salmon for 60 days on thrombotic markers: (vwf, P-selecting, platelet microparticle: [CD41, CD62P, and PS-Annexin-V]);
iii. To determine and compare means between before and after treatment of EPA+DHA from YSS and salmon for 60 days on cardiovascular markers**:** (Leptin, sCD40L, IL-1β, VCAM-1, MCP-1, IL-6, TNF-α);
iv. To determine and compare means between before and after treatment of EPA+DHA from YSS and salmon for 60 days on target therapeutic markers**:** (NF-kB and PPAR-γ);
v. To determine and compare means between before and after treatment of EPA+DHA from YSS and salmon with on effect of EPA+DHA time and interaction on an atherosclerotic, thrombotic, and CVD risk and target therapeutic markers;

vi. To propose a novelty pathway of YSS (EPA+DHA) mechanism of anti-inflammatory and cardio-protection.

1.5 Research hypothesis

i. H_0: There is no significant difference between means of EPA+DHA from YSS and salmon on atherosclerotic, thrombotic, and CVD risk markers among healthy overweight subjects;
ii. H_A: There are significant differences between means of EPA+DHA from YSS and salmon on an atherosclerotic, thrombotic, and CVD risk markers among healthy overweight subjects;
iii. H_0: There are no significant difference between means of EPA+DHA from YSS and salmon with effects of time and interaction on atherosclerotic, thrombotic, and CVD risk markers among healthy overweight subjects;
iv. H_A: There are significant differences between means of EPA+DHA from YSS and salmon, with effects of time and interaction on atherosclerotic, thrombotic

1.6 Conceptual frameworks and CVD risk markers among healthy overweight subjects.

The framework of the study objective; as atherosclerosis factor, thrombotic factor, and CVD factor as (YSS-baseline; salmon-baseline) dependent variable and treatment with (YSS and Salmon) as an independent variable; That EPA+DHA from YSS and salmon modify and modulates platelet cells membrane, to decrease platelet activation to decrease the platelet interaction with other cells to protect against thrombosis and CVD.

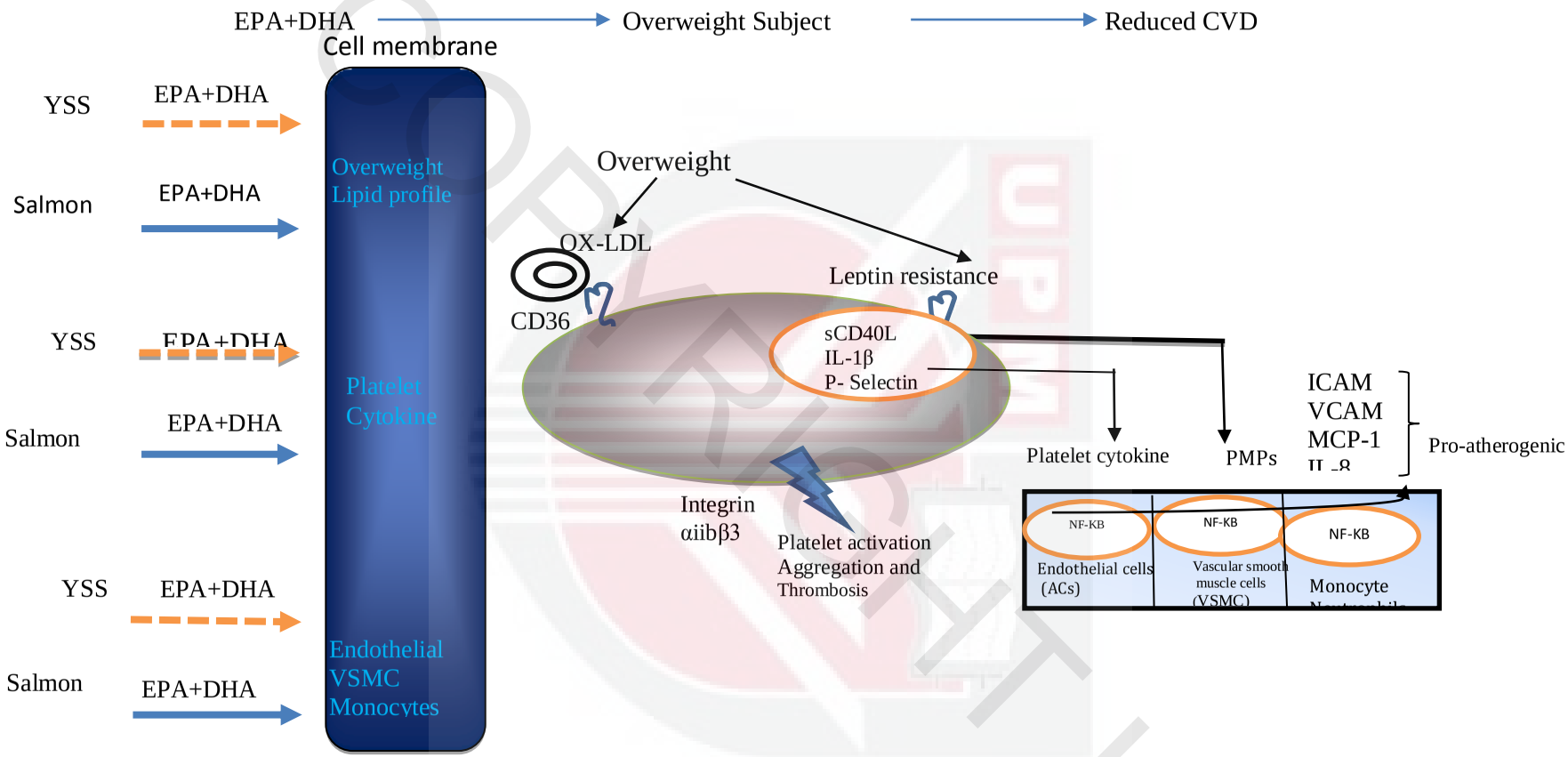

Figure 1.1 : Conceptual framework of the study to manage the CVD risk factor via EPA+DHA from YSS and Salmon: Summarized overweight excessive LDL-C and leptin resistance that activate Platelet to release platelet cytokine and platelet microparticle (PMPs) both damaged the endothelial cells and signal via the vascular endothelial cells, vascular smooth muscle cells(VSMC), Neutrophils, and Monocytes to activates NF-kB, to produce pro-atherogenic protein such as ICAM, VCAM MICP-1, TNF-α, IL-6, IL-8. YSS and Salmon may harmonize platelet and endothelial cells phospholipid membrane to modify the cellular receptors and reduced CVD

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