UNIVERSITI PUTRA MALAYSIA

EXPRESSION ANALYSIS OF □-TTP, PI-TP AND SPF GENES IN H2O2-INDUCED HUVECs AND NEURONAL CELLS SUPPLEMENTED WITH □-TOCOPHEROL AND TOCOTRIENOL-RICH FRACTION

AISHATU ALI CHIROMA

FPSK(M) 2017 46

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By

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Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfillment of the Requirements for the Degree of Master of Science

May 2017

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Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfillment of the requirement for the Degree of Master of Science

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May 2017

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Faculty : Medicine and Health Science

Vitamin E has 8 isoforms namely; α, β, γ, δ -tocopherols (TCP) and α, β, γ, δ -tocotrienols (TCT). Natural α-tocopherol (α-TCP) but not TCT is preferentially retained in the human body. Studies showed that α-tocopherol transfer protein (α-TTP) is responsible to bind α-TCP for cellular uptake. However, α-TTP has strong specificity and high affinity for α-TCP and poorly binds to α-tocotrienol. Despite of the nature of α-TTP discriminating tocotrienol, population with palm oil as primary source of lipid consisting of 75% TCT and 25% TCP which is taken daily, however has no alarming deficiency reported. Therefore, interest on mechanism of uptake of vitamin E is addressed in this study. The purposes of this study were to examine the modification of *α-TTP* together with other vitamin E binding related genes in regulating vitamin E uptake in neuronal cell and HUVECs under resting and oxidative stress. Oxidative stress was induced with H_2O_2 for one hour followed by supplementation with different ratios of α-TCP and Tocotrienol Rich Fraction (TRF) for 4 hours. Likewise, both cells were treated with vitamin E without oxidative stress. Real-time PCR was used to determine expression levels of the genes. The cellular levels of vitamin E were quantified by HPLC as the index of cell bioavailability. The study showed that expression levels of genes encoding the vitamin E binding proteins, including α-tocopherol transfer protein (α-TTP/*TTPA*), Supernatant protein factor (SPF/*SEC14L2*) and Phosphatidyl inositol transfer protein (PI-TP/*PI-TPNA*) in 0% α-TCP positively correlated to the cellular levels of vitamin E in resting neuronal cells and HUVECs under oxidative stress. The expression levels of all genes examined were different in the two cells under oxidative stress, which may contribute to cellular vitamin E content. However, in resting neuronal cells and HUVECs cells the levels were similar. Between the two cells, HUVECs was more sensitive to oxidative stress, which induced gene expressions of *TTPA, SEC14L2*, and *PI-TPNA*. Altogether, these results suggest that the regulation of *TTPA*, *SEC14L2* and *PI-TPNA* genes in the HUVECs and the neurons, affects the distribution of vitamin E in endothelial and

neuronal cells. Furthermore, it is reasonable to postulate that under conditions of oxidative stress, increased gene levels would cause increased α-TCP secretion from the neuronal cells or HUVECs thereby proteins could be modified and in the absence of α-TCP they may switch to take up TCT. Generally, our data suggests that probably the expression levels of vitamin E transport proteins might influence cellular concentrations of vitamin E levels in neuronal cells and HUVECs.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk Ijazah Master Sains

ANALISA EKSPRESI α-*TTP, PI-TP* DAN *SPF* GEN DI DALAM SEL HUVECs DAN NEURONAL YANG DI ARUH OLEH H_2O_2 DAN DISUPPLEMENTASIKAN DENGAN α-TOKOFEROL DAN FRAKSI KAYA TOKOTRIENOL

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Vitamin E mempunyai 8 isoforms iaitu; α, β, γ, δ -tocopherols (TCP) dan α, β, γ, δ-tocotrienols (TCT). Secara semulajadi, α-tokoferol (α -TCP) tetapi tidak TCT adalah banyak terkumpul dalam badan manusia. Kajian telah menunjukkan bahawa protin pemindah α-tokoferol (α-TTP) bertanggungjawab untuk mengikat α-TCP untuk pengambilan selular. Walau bagaimanapun, α-TTP mempunyai kekhususan yang kukuh dan pertalian tinggi untuk α-TCP dan kurang mengikat kepada α-tocotrienol. Walaupun sifat α-TTP mendiskriminasi tocotrienol, penduduk yang menggunakan minyak sawit sebagai sumber utama lipid yang terdiri daripada 75% TCT dan 25% TCP yang diambil setiap hari, bagaimanapun tidak dilaporkan mempunyai kekurangan yang membimbangkan. Oleh itu, rasa ingin tahu mengenai mekanisme pengambilan vitamin E dijelaskan dalam kajian ini.Tujuan kajian ini adalah untuk mengkaji pengubahsuaian α-TTP dan vitamin E pengikat protin yang lain yang berkaitan dalam mengawal-selia vitamin E untuk pengambilan dalam sel neuron dan HUVECs di bawah keadaan rehat dan tekanan oksidatif. Tekanan oksidatif telah didorong dengan hydrogen peroksida (H_2O_2) selama sejam diikuti dengan rawatan menggunakan nisbah yang berbeza daripada α-TCP dan TRF selama 4 jam. Begitu juga, kedua-dua sel telah dirawat dengan vitamin E tanpa tekanan oksidatif dan perbezaan antara kedua-dua eksperimen telah dibandingkan. Masa nyata- *PCR* telah digunakan untuk menentukan tahap ekspresi gen. Paras selular vitamin E telah diukur dengan cecair kromatografi prestasi tinggi (HPLC) sebagai indeks bioavailabiliti sel. Kajian ini menunjukkan bahawa tahap ekspresi vitamin E pengikat protin, termasuk protin pemindah α-tokoferol *(α-TTP / TTPA*), faktor protein Supernatan *(SPF / SEC14L2*) dan protein pemindah phosphatidyl inositol *(PI-TP / PI-TPNA)* dalam 0 % α-TCP positif kepada tahap selular vitamin E sel neuron dalam keadaan rehat dan HUVECs dalam tekanan oksidatif. Tahap ekspresi semua gen yang diuji adalah berbeza dalam kedua-dua sel di bawah tekanan oksidatif, yang menyumbang kepada

kandungan vitamin E selular. Walau bagaimanapun, dalam sel-sel neuron dan sel-sel berehat HUVECs, tahapnya adalah sama. Antara kedua-dua sel-sel, HUVECs adalah lebih sensitif kepada tekanan oksidatif yang merangsang ekspresi gen *TTPA, SEC14L2* dan *PI-TPNA*. Kesimpulannya, keputusan ini menunjukkan bahawa regulasi gen *TTPA, SEC14L2 dan PI-TPNA* dalam sel HUVECs dan neuron, memberi kesan kepada pengedaran vitamin E dalam endothelial dan sel neuron. Tahap ekspresi protin pengikat vitamin E, di 0% α-TCP positif kepada tahap selular vitamin E dalam keadaan rehat sel neuron dan HUVECs di bawah tekanan oksidatif. Tambahan pula, ia adalah postulasi munasabah bahawa di bawah keadaan tekanan oksidatif, peningkatan paras gen akan menyebabkan peningkatan rembesan α-TCP dari sel-sel neuron atau HUVECs yang menyebabkan protein terubah dan dalam ketiadaan α-TCP, mereka boleh beralih ke mengambil TCT. Secara amnya, data kami menunjukkan bahawa mungkin tahap ekspresi protein pengangkut vitamin E boleh mempengaruhi kepekatan vitamin E dalam HUVECs dan sel neuron.

ACKNOWLEDGEMENTS

All praise to Allah, the Almighty with His infinite mercy for granting me the opportuinity, health and strength to earn a successful completion of my masters program. I am thankful for His blessings on me in every aspect of my life and for making this journey a success.

I would like to acknowledge my advisor Dr. Huzwah Binti Khaza'ai for taking the time to read my thesis word by word and corrected me to make sure that things were done the right way. I will be forever grateful for her patience with my writing, which progressed slower than mastering bench techniques. I believe I will leave the master program as a well-rounded scientist because of her commitment to my success. I would also like to express my deepest gratitude to my co- supervisor, Dr. Roslida for her kind support. I would like to thank the rest of my beloved lecturer, Dr. Abdah Md. Akim, and Assoc. Prof.Dr. Sokhini b.Abd.Mutalib

There are many people I need to extend my sincere gratitude to for their help in me earning my masters. Najwa was a key contributor to my second parameter. Her help with getting the HPLC experiments rolling was crucial to the success of this project. I would like to thank my friends Amirah, Aminah, Henna, Najwa, Asma, Afifah and Nur'izzati, my past and present lab-mates with whom I worked with day in and day out.

A sincere gratitude and appreciation goes to Faculty of Medicine and Health Science, Universiti Putra Malaysia, the place that has granted me the opportunity and amenities to amass the essential practical skills and the keen in fulfilling the research. A special note of thanks goes to all staffs of the Biomedical department, Biochemistry, Cell signaling and Nutrition Laboratory for their constructive assistance while grasping the handiness laboratory tasks.

I cannot express how fortunate I am to have such a remarkable family. Their unbelievable love and support played a critical role in me completing this journey. They were always there when I needed a motivation. To say I have the best family is an understatement. I want to acknowledge my father and my mother; I know they instilled in me many values and characteristics that have shaped the person I am today. I also want to acknowledge my step mum and my sister for their love and support throughout the journey.

I certify that a Thesis Examination Committee has met on 17 May 2017 to conduct the final examination of Aishatu Ali Chiroma on her thesis entitled "Expression Analysis of *α-TTP, PI-TP* and *SPF* Genes in H_2O_2-Induced HUVECs and Neuronal Cells Supplemented with α-Tocopherol and Tocotrienol-Rich Fraction" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the Master of Science.

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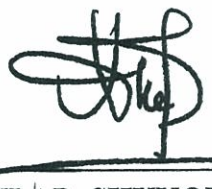

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This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfillment of the requirement for the degree of Master of Science. The members of the Supervisory Committee were as follows:

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Name of Chairman of Supervisory Committee: Dr. Huzwah Binti Khaza'ai

Signature: _____
Name of Member of Supervisory Committee: Associate Professor Dr. Roslida Binti Abdul Hamid

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LIST OF ABBREVIATIONS

%	Percentage
±	More or less
μg	Microgram
μM	Micro molar
°C	Degree Celsius
α-TCP	Alpha tocopherol
α-TCT	Alpha tocotrienol
α-TTP	Alpha tocopherol transfer protein
ABC A1	ATP-binding cassette transporter subtype A1
ANOVA	Analysis of variance
APO A	Apo lipoprotein A
AVED	Ataxia with vitamin E deficiency
Caco-2	Colorectal adenocarcinoma cells
cDNA	Complementary DNA
CEHC	Carboxyethyl hydroxyl chromanol
COX2	Cyclooxygenase 2
CRAL-TRIO	Cellular retinal TRIO
CRALBP	Cellular retinaldehyde binding protein
CSF	Cyclooxygenase 2
CYP450	Cytochrome p450
DEPC	Diethyl pyrocarbonate
DMSO	Dimethyl sulfoxide
DMBA	7,12-dimethylbenz(a)anthracene

DNA	Deoxyribonucleic acid
E	Efficiency
ETS	Environmental tobacco smoke
FBS	Fetal Bovine Serum
GAPDH	Glyceraldehyde 3-phosphate dehydrogenase. Gene: *GAPDH*
H_2O	Water
H_2O_2	Hydrogen peroxide
HDL	High density lipoprotein
HIF	Human intestinal fibroblast
HMG-COA	5-Hydroxy-3-methylglutaryl-coenzyme A reductase
HL-60	Human promyelocytic leukemia cells
hTAP	Human tocopherol associated protein
IL-1β	Interleukin-1β
IL-8	Interleukin-8
IHH	Interleukin-8
INOS	Inducible nitric oxide synthase
kDA	Kilo Dalton
LDL	Low density lipoprotein
LTB4	Leukotriene B4
LTC4	Leukotriene C4
MEM	Minimum Essential Media
MDA	Methylenedioldioxyaphatamine
MCD	Methionine choline deficiency
MPP^+	1-methyl-4-phenylpyridinium

NF-KB	Nuclear factor kabba B
NO	Nitrogen oxide
PGD2	Prostaglandin D2
PGE2	Prostaglandin E2
PI-TPNA	Phosphatidyl inositol transfer protein alpha gene
PI-TP	Phosphatidyl inositol transfer protein
PK	Protein kinase
PK13γ	Protein kinase B gamma
RAW264.7	Mouse leukemia monocyte macrophage
RNA	Ribonucleic acid
SOD	Superoxide dismutase
STZ	Streptozotocin
TBARS	Thiobarbituric reactive substance
TNF-α	Necrotic factor alpha
WML	White matter lesion
VLDL	Very low density lipoprotein
VEGF	Vascular endothelial growth factor

CHAPTER 1

INTRODUCTION

1.1 Background of the study

Vitamin E comprises of two forms of isomers, which includes tocopherol (TCP) and tocotrienol (TCT). It is considered as a major fat-soluble antioxidant present in the plasma of human. Both TCP and TCT forms each consists of four subtypes α, β, γ, and δ-TCP and α, β, γ, and δ-TCT. TCP and TCT are similar in their structure with only the difference on its phytyl tail. TCP has saturated tail while TCT has unsaturated tail. Despite of similarities in their chromanol ring and differences in their side chain, these subtypes differ from each other in their bio potency (Azzi et al., 2003; Traber et al., 1996) due to the number and location of methyl groups on the chromanol ring. In fact, the different forms perform different biological activities (Jiang, 2014). All the eight forms are strong antioxidants, which have the ability to scavenge and quench free radicals by donating an electron and neutralize the reactivity of free radicals. In addition to their antioxidant activities, studies showed the involvement of vitamin E in other functions such as immune function, cell signaling, regulation of gene expression, cell Homeostasis, and other metabolic processes (Cardenas & Ghosh, 2013; Wu & Meydani, 2014; Jiang, 2014; Santolim et al., 2017). Natural α-tocopherol (α-TCP) but not TCT is preferentially retained in the human body for human physiological functions, which is available in high amount in mammalian tissues.

Absorption of vitamin E starts with esterification of vitamin E by pancreatic esterase and bile acids are needed for the micellarization of these vitamin E-containing dietary lipids. Vitamin E moves into the blood circulation via the lymphatic system with the help of chylomicrons. Chylomicrons then deliver it to the liver for further processing for metabolism. In the liver, α-TCP is seperated from the other non α-TCP by the α-TTP. The hepatocytes actively retain α-TCP levels whereas the other isoforms of vitamin E which are not bound to α-TTP are metabolized and excreted. The present of α-TTP in the liver preferentially facilitates the transport of α-TCP to the plasma membrane and incorporates α-TCP into nascent lipoproteins that are secreted into the circulation. The lipoproteins are secreted by the liver and circulated throughout the body, transporting α-TCP to other tissues through the blood circulation (Schmozl, et al., 2016). In addition, α-TCP is easily exchanged between membrane phospholipids and lipoproteins, which may contribute to its tissue delivery and uptake.

Several studies confirmed that α-TCP status could regulate α-TTP expression levels *in vivo* studies (Shaw et al., 1998; Thakur et al., 2010). The authors demonstrated that deficiency of α-TCP resulted in low levels of α-TTP (Shaw et al., 1998; Thakur et al., 2010). Where as in other demonstration vitamin E repletion reduced α-TTP levels while depletion did not change α-TTP levels though mRNA level increased. Furthermore, Several studies also confirmed that α-TCP status and oxidative stress

could regulate α-TTP expression although the data are inconclusive. Many *in vivo* (Usenko et al., 2008; Miyazaki et al., 2012; Tikitani et al., 2014) and *in vitro* (Ulatowski et al., 2012; Etzl et al., 2012) studies have shown that the presence of oxidative stress led to up regulation of α-TTP levels or has demonstrated the involvement of oxidative stress in the up regulation of α-TTP. On the other hand, some in vivo studies reported that oxidative stress down regulated α-TTP (Miyazaki et al., 2014; Bella et al., 2006).

There are several factors that can cause oxidative stress; hydrogen peroxide is one of it. Under normal condition it serves as intracellular messenger and acts as cell signaling molecule. However, excess levels of this molecule induces excitotoxicity in neuronal and endothelial cells which eventually leads to oxidative stress. *In vitro* H_2O_2- toxicity is a well-established model for generating oxidative stress. H_2O_2 can exert its toxic effects through the formation of highly reactive hydroxyl radical (OH). Oxidative stress occurs when there is imbalance between the generation of free radicals and the ability of antioxidant systems in the body to neutralize their harmful effects.

α-TTP is a cytosolic protein that has been shown to have a role in vitamin E uptake. It selectively binds α-TCP for cellular uptake where it has strong specificity and high affinity for α-TCP and poorly binds to α-TCT. This current study suggests that in severe deficiency of α-TCP, the transport proteins may be modulated. Understanding the concerted effort between proteins involved in vitamin E uptake in neuronal and endothelial cells warrants further investigation. Therefore, in addition to α-tocopherol transfer protein (α-TTP), two other proteins having a strong relationship in vitamin E uptake; Phosphatydylinositol transfer protein (PI-TP) and supernatant protein factor (SPF) that are involved in vitamin E homeostasis became the interest of this study suggesting new insight into the uptake function of the proteins towards other vitamin E isomers.

This study aimed to elucidate α-TTP, PI-TP and SPF in regulating vitamin E uptake in neuronal cell and HUVECs in resting and under oxidative stress upon supplementation with different ratios of α-TCP and TRF and to understand how oxidative stress and deficiency of α-TCP involved in modulating the absorption of tocotrienol.

1.2 Problem of research

Palm oil, which is the main source of vitamin E among the populace of Malaysia, consists of 75% tocotrienol and 25% tocopherol. However, no alarming deficiency of vitamin E has been reported even though α-TTP selectively binds α-TCP separating from the other 7 isoforms. Therefore, interest on how specific is α-TTP in maintaining vitamin E homeostasis in plasma became the interest of this study. The importance of α-TCP homeostasis became apparent when it was observed that error in α-TTP gene

due to mutations led to ataxia with vitamin E deficiency (AVED), an autosomal recessive disease in which degeneration of neurons resulted in progressive spinocerebellar ataxia (Gotoda et al., 1995) and retinitis pigmentosa (Yokota et al., 1997).

1.3 Hypothesis

α-TTP and other associated vitamin E proteins: PI-TP and SPF are the transport proteins that have strong association in vitamin E uptake.

1.4 Research Objectives

1.4.1 General Objectives

To study the mechanism of *α-TTP*, *PI-TP* and *SPF* genes in H_2O_2 induced Neuronal cells and HUVECs supplemented with different ratios of α-TCP and TRF.

1.4.2 Specific objectives

- To determine IC_{20} of H_2O_2 in Neuronal cells and HUVECs
- To determine the expression of *TTPA, PI-TPNA* and *SEC14L2* genes with or without H_2O_2 supplemented with different ratios of α-TCP and TRF and to compare the expression between the two cell groups.
- To determine the cellular uptake of α-TCP and TRF in with (oxidative stress) or without H_2O_2 (Resting cells) neuronal cells and HUVECs.

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