UNIVERSITI PUTRA MALAYSIA

IMMUNOMODULATORY EFFECTS OF PALM OIL-DERIVED DELTA-TOCOTRIENOL ON MICROGLIA RESPONSES

TAN SHI WEI

FPSK(p) 2018 9

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By

TAN SHI WEI

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Doctor of Philosophy

December 2017

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Dedicated to my lovely family and my beloved husband

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

IMMUNOMODULATORY EFFECTS OF PALM OIL-DERIVED DELTA-TOCOTRIENOL ON MICROGLIA RESPONSES

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December 2017

Chair: Sharmili Vidyadaran, PhD
Faculty: Medicine and Health Sciences

Microglia are the main immunocompetent cells of the central nervous system (CNS). The chronic inflammatory responses of microglia can lead to significant neuronal damage. Thus, strategies to control microglia activation provide an alternative therapeutic approach for neuroinflammatory diseases. Vitamin E, namely the tocopherols and tocotrienols, are potent antioxidant and anti-inflammatory compounds. Importantly, tocotrienols confer higher protection against glutamate-induced neurotoxicity compared to tocopherols. BV2 microglia pre-treated with delta-tocotrienol (δ-tocotrienol) showed highest reduction in NO production compared to treatment with alpha- (α-) and gamma- (γ-) isomers. This current study explores the modulatory function of δ-tocotrienol on microglial inflammatory responses, mainly by using primary mouse microglia cultures.

Primary mouse microglia cells were treated with δ-tocotrienol at various concentrations (10, 12.5, 15, 17.5 and 20 μg/mL) 24 hrs prior to co-stimulation with lipopolysaccharide (LPS)/interferon-gamma (IFN-γ) (0.5 μg/mL; 50 ng/mL). The two highest concentrations of δ-tocotrienol (17.5 and 20 μg/mL) were found to reduce NO levels most by 50% and 58% ($p<.05$), respectively. Hence, these doses were chosen for downstream experiments. The effects of δ-tocotrienol on the inflammatory phenotype of primary microglia including the production of inflammatory cytokines, eicosanoids as well as expression of the CD40 co-stimulatory molecule, were determined.

It was found that the NO reduction by δ-tocotrienol was not attributed to NO scavenging, but to the down-regulation of inducible nitric oxide synthase (iNOS) mRNA (-3.7 fold; $p<.05$) in primary microglia. In BV2 microglia, δ-tocotrienol reduced iNOS protein expression by 3-fold ($p<.05$).

δ-tocotrienol also exhibited prominent inhibitory effects on primary microglial production of interleukin-1β (IL-1β) by 77.6%, which was coupled with down-regulation of IL-1β mRNA expression by 6.6-fold ($p<.05$). However, primary microglial expression of both tumour necrosis factor-alpha (TNF-α) and IL-6 was not affected by δ-tocotrienol, be it at the mRNA or protein level. Production of the anti-inflammatory cytokine (IL-10) was not detectable. Production of an important eicosanoid, prostaglandin E2 (PGE2), was significantly reduced by δ-tocotrienol in activated microglia by 78.2%. This was accompanied by a down-regulation of cyclooxygenase (COX)-2 mRNA expression by 3.3-fold ($p<.05$), but not the expression of COX-1. Despite the undetectable levels of leukotriene B4 (LTB4) in primary microglia, δ-tocotrienol significantly down-regulated the mRNA expression of 5-lipoxygenase (5-LOX) in activated primary microglia cells by 3.6-fold ($p<.05$). Unexpectedly, δ-tocotrienol increased the CD40 microglial activation marker in primary microglia, indicating the heterogeneous effects of δ-tocotrienol on microglial responses.

Finally, HPLC analysis revealed that δ-tocotrienol uptake by BV2 microglia was detected as early as five mins after administration, and relatively low amounts of intracellular δ-tocotrienol (14% of the administered δ-tocotrienol) were required to exert the observed beneficial effects on microglia observed. These findings indicate that fast incorporation and retention of δ-tocotrienol in microglia are most likely to be main factors for all modulatory effects of δ-tocotrienol observed in this study. Taken together, the findings from this project revealed the ability of δ-tocotrienol in modulating microglial inflammatory responses via reduction of the pro-inflammatory mediators NO, IL-1β and PGE2. The modulatory effects of δ-tocotrienol did not include reduction of the pro-inflammatory cytokines, TNF-α and IL-6 nor increased the anti-inflammatory cytokine IL-10. This indicates δ-tocotrienol is a potentially therapeutic substance for neuroinflammatory diseases.

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

KESAN IMUNOMODULATORI DELTA-TOKOTRIENOL DARIPADA MINYAK KELAPA SAWIT TERHADAP TINDAKBALAS MIKROGLIA

Oleh

TAN SHI WEI

Disember 2017

Pengerusi: Sharmili Vidyadaran, PhD
Fakulti: Perubatan dan Sain Kesihatan

Mikroglia adalah sel imunomampu yang utama dalam sistem saraf pusat (CNS). Tindak balas keradangan kronik mikroglia boleh mengakibatkan kerosakan saraf yang nyata. Oleh itu, strategi untuk mengawal pengaktifan sel mikroglia ini menyediakan pendekatan terapeutik alternative bagi merawat penyakit keradangan saraf. Vitamin E, termasuk tokoferol dan tokotrienol merupakan bahan antioksida dan kompaun anti-radang yang kuat. Namun, tokotrienol memberikan perlindungan yang lebih banyak terhadap keneurotoksikan yang dirangsang oleh glutamat berbanding tokoferol. Pra-rawatan BV2 mikroglia dengan menggunakan delta-tokotrienol (δ-tokotrienol) menunjukkan kesan perencatan terhadap penghasilan nitrik oksida (NO) lebih berkesan berbanding pra-rawatan yang menggunakan isomer alfa- (α-) dan gamma- (γ-). Maka, kajian ini dilanjutkan untuk memberi penjelasan tehadap kesan pengawalan δ-tokotrienol terhadap gerak balas inflamasi mikroglia dengan mengunakan kultur mikroglia primer daripada tikus.

Mikroglia primer dirawat dengan menggunakan 5 kepekatan δ-tokotrienol yang berbeza (10, 12.5, 15, 17.5 and 20 μg/mL) selama 24 jam sebelum dirangsang bersama menggunakan lipopolisakarida (LPS)/interferon-gamma (IFN-γ) (0.5 μg/mL; 50 ng/mL). δ-tokotrienol pada dua kepekatan tertinggi (17.5 dan 20 μg/mL) dapat mengurangkan paras NO paling banyak dengan 50% dan 58% ($p<0.05$) masing-masing. Maka, kedua-dua kepekatan tersebut telah dipilih untuk eksperimen yang seterusnya. Kesan δ-tokorienol terhadap fenotip keradangan mikroglia primer termasuk penghasilan sitokin keradangan dan eicosanoid serta ekspresi molekul rangsangan bersama CD40 telah ditentukan dalam kajian ini.

Berdasarkan kajian, kesan penurunan NO oleh δ-tokotrienal ini tidak disebabkan oleh tindakan skaveng NO, tetapi adalah berkaitan dengan penurunan tahap kawalatur ekspresi mRNA nitrik oksida sintase (iNOS) (-3.7 kali ganda; $p<0.05$) dalam mikroglia primer. δ-tokotrienol juga didapati menurunkan ekspresi protein iNOS sebanyak 3 kali ganda ($p<0.05$) dalam sel abadi BV2 mikroglia.

δ-tokotrienol juga menunjukkan kesan ketara perencatannya pada penghasilan interleukin-1β (IL-1β) oleh mikroglia primer sebanyak 77.6%, dengan mengurangkan pengawalaturan ekspresi mRNA IL-1β sebanyak 6.6 kali ganda ($p<.05$). Walau bagaimanapun, δ-tokotrienol gagal memodulasikan penghasilan dan ekspresi mRNA nekrosis tumor faktor-alfa (TNF-α) dan IL-6 dalam mikroglia primer. Selain itu, penghasilan dan ekspresi mRNA sitokin anti-radang IL-10 tidak dapat dikesan dalam kajian ini. Penghasilan eicosanoid utama, prostaglandin E2 (PGE2) telah ditindas oleh δ-tokotrienol dalam mikroglia yang telah dirangsang bersama sebanyak 78.2% melalui penurunan tahap kawalatur ekspresi mRNA cyclooxygenase (COX)-2 sebanyak 3.3 kali ganda ($p<0.05$), tanpa menjejaskan ekspresi berterusan COX-1. Walaupun paras leukotriene B4 (LTB4) dalam mikroglia primer tak dapat dikesan, δ-tokotrienol juga menurunkankan pengawalaturan ekspresi mRNA 5-lipoxygenase (5-LOX) dalam mikroglia sebanyak 3.6 kali ganda ($p<0.05$). Namun begitu, δ-tokotrienol meningkatkan kandungan penanda aktivasi mikroglia CD40 , dan ini menunjukkan kehadiran kesan heterogen δ-tokotrienol pada tindakbalas mikroglia.

Akhir sekali, analisis HPLC menunjukkan δ-tokotrienol yang diambil oleh mikroglia dikesan seawal 5 minit selepas penambahan, dan sedikit kuantiti intraselular δ-tokotrienol (14% daripada jumlah δ-tocotrienol yang ditambahkan) diperlukan untuk memberikan kesan yang baik terhadap mikroglia. Ini menunjukkan inkorporasi secara cepat serta retensi δ-tokotrienol dalam sel mikroglia merupakan faktor penting yang menyebabkan kesan modulasi δ-tokotrienol. Secara keseluruhannya, penemuan daripada projek ini menunjukkan keupayaan δ-tokotrienol dalam mengehadkan tindakbalas keradangan mikroglia melalui penurunan pengantara pro-radang seperti NO, IL-1β serta PGE2. kesan pengawalan δ-tokotrienol tidak termasuklah dalam penurunan TNF-α dan IL-6 pro-radang dan kenaikan penghasilan IL-10 yang anti-radang. Oleh itu, penemuan ini boleh menjadikan δ-tokotrienol sebagai satu agen terapeutik yang berkebolehan untuk merawat penyakit keradangan saraf.

ACKNOWLEDGEMENTS

First of all, I would like to express my deepest and most sincere gratitude to my dear supervisor, Assoc. Prof. Dr. Sharmili Vidyadaran, for her wise advice, guidance, encouragement and countless contribution throughout my whole PhD candidature. She is a mentor who willing to train me and inspires me to be a better scientist. She is also a friend to me, who never fails to take her precious time to listen to all the problems I faced during the candidature, be it an experimental one or my personal problems. *"Thank you so much, Dr. Shali!"*

A special note of appreciation also goes to Dr. Huzwah, Dr. Wong Jia Woei and Prof. Dr. Daud for their contribution in giving valuable ideas and professional advice to make this project better in quality. My acknowledgement also extended to all my fellow lab mates in Immunology laboratory including Shins, Tong, Zul, Catherine, Iris, Stephnie, Le Jie, Randy and who provide endless support and accompany to make these years an enjoyable experience for me. Many thanks to the Immunology lab staff including Kak Marsitah, Kak Aisyah, Kak Ezura and Mr. Anthony for their assistance in the lab.

Next, I would like to thank Excelvite Sdn. Bhd. for providing me with the precious tocotrienol fragments and also MyBrain15, KPT, Malaysia for my personal financial support.

My heartfelt thanks to my family members especially my parents for their love, dedication and endless moral support. Last but most importantly, Pei Shen—my husband, thank you for your unlimited love and believing in me that I can achieve this!

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:

Sharmili Vidyadaran, PhD
Associate Professor
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Chairman)

Daud Ahmad Bin Israf Ali, PhD
Professor
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Member)

Huzwah Binti Khaza'ai, PhD
Senior Lecturer
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Member)

Wong Jia Woei, PhD
Research and Development Manager
Hovid Research Sdn. Bhd.
Malaysia
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Name of
Member of
Supervisory
Committee: Daud Ahmad Bin Israf Ali

Signature: _____
Name of
Member of
Supervisory
Committee: Huzwah Binti Khaza'ai

Signature: _____
Name of
Member of
Supervisory
Committee: Wong Jia Woei

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RT	room temperature
1X	one time
AA	arachidonic acid
AD	Alzheimer's disease
APCs	antigen presenting cells
$A\beta_{25-35}$	beta amyloid
BBB	blood-brain barrier
BSA	bovine serum albumin
CNS	central nervous system
COX	cyclooxygenase
DAPI	4',6-diamidino-2-phenylindole
dH_2O	distilled water
DMEM	Dulbecco's Modified Eagle Medium
DMSO	dimethyl sulfoxide
EAE	experimental autoimmune encephalomyelitis
EDTA	ethylenediamine tetraacetic acid
EtOH	ethanol
FBS	fetal bovine serum
FITC	fluorescein isothiocyanate
H_2O	water
HRP	horseradish peroxidase
IFN-γ	interferon-gamma
IL	interleukin
iNOS	inducible nitric oxide synthase
LOX	lipoxygenase
LPS	lipopolysaccharide
LT	leukotriene
LTB4	leukotriene B4
MFI	median fluorescence intensity
MS	multiple sclerosis
$NaNO_2$	sodium nitrite
NED	*N*-1-napthylethylenediamine dihydrochloride
NO	nitric oxide
NO_2^-	nitrite
PBS	phosphate buffer saline
PE	phycoerythrin
PG	prostaglandin
PGE2	prostaglandin E2
PTIO	2-Phenyl-4,4,5,5-tetramethylimidazoline-1-oxyl 3-oxide
rpm	revolutions per minute
SD	standard deviation
SDS	sodium dodecyl sulfate
SNP	sodium nitroprusside
Th1	T helper cell type 1
TNF-α	tumour necrosis factor-alpha

TLR-4	toll-like receptor 4

CHAPTER 1

INTRODUCTION

Microglia are central nervous system (CNS)-specific macrophages and are responsible for initiating inflammatory reactions within this microenvironment. They are derived from primitive myeloid progenitors that migrate to the brain from the yolk sac during embryogenesis (Ginhoux et al., 2010). Microglia are therefore distinct from bone marrow (BM)-derived macrophages (Schulz et al., 2012). In a healthy brain, microglia retain a ramified morphology with highly motile processes which enable them to monitor the entire brain within a few hours (Nimmerjahn *et al.*, 2005). They move around to screen for dead and damaged neurones, invading microorganisms and endogenous disease proteins (Hanisch & Kettenmann, 2007).

In response to various types of CNS insults, microglia assume a pro-inflammatory phenotype by shifting from a ramified to amoeboid morphology, proliferating and releasing pro-inflammatory mediators such as cytokines, chemokines, reactive oxygen/nitrogen species, eicosanoids as well as performing phagocytic activity. These responses are primarily triggered for the beneficial purpose of resolving a CNS challenge and are collectively regarded as microgliosis (Streit *et al.*, 1999). However, activated microglia have been implicated in the pathology of various neurodegenerative diseases. Elevated levels of neurotoxic factors such as prostaglandin E2 (PGE2), interleukin-1β (IL-1β), tumour necrosis factor-α (TNF-α), nitric oxide (NO) and super radical species, released by activated microglia upon inflammatory stimulation can cause bystander damage to neurones. Therefore, along with the primary cause of CNS disease, the chronic inflammatory responses of activated microglia are now also viewed as an important pathophysiological component of inflammatory and degenerative CNS conditions. This underscores the importance of modulating activation of microglia in reducing inflammation and tissue damage within the CNS.

Tocotrienols, which are one of the subfamilies of vitamin E, are divided into four chemically distinct isoforms and assigned as alpha (α), beta (β), gamma (γ) and delta (δ). They did not gain real attention in therapeutics until they were discovered to have better ameliorative effects over tocopherols, for oxidative stress (Serbinova *et al.*, 1991), cancer (McIntyre *et al.*, 2000; Inokuchi *et al.*, 2003), inflammation (Wu *et al.*, 2008; Yam *et al.*, 2009) and neurotoxicities (Sen *et al.*, 2000; Osakada *et al.*, 2004; Shichiri *et al.*, 2007). For instance, nanomolar concentrations of α-tocotrienol, but not α-tocopherol, were shown to provide full

neuroprotection from a glutamate challenge (Sen *et al.*, 2000; Khanna *et al.*, 2003). Sen and colleagues (2000) also revealed that α-tocotrienol exerts neuroprotective effects via modulation of neurone cell signalling transduction process. This indicates that tocotrienols can regulate cellular events by modulating cell signal transduction processes which are independent of their antioxidant property. Furthermore, tissue bioavailability of tocotrienols has been addressed by numerous studies which showed that tocotrienols are detectable in the brain and spinal cord of rats (Roy *et al.*, 2002; Khanna *et al.*, 2005a; Patel *et al.*, 2006), dogs (Rink *et al.*, 2011) and even human brains (Patel *et al.*, 2012).

Studies have also demonstrated the anti-inflammatory effects of tocotrienols on macrophages (which exhibit inflammatory responses similar to microglial cells) including the reduction of pro-inflammatory mediators such as NO, PGE2, inducible nitric oxide synthase (iNOS) and pro-inflammatory cytokines (TNF-α, IL-4, and IL-8) (Wu et al., 2008; Yam et al., 2009). Delta-tocotrienol was found to be the most effective in reducing the production of LPS-induced pro-inflammatory mediators in macrophages, as compared to α-tocotrienol, γ-tocotrienol and the tocotrienol-rich fragment (TRF) (Yam et al., 2009; Qureshi et al., 2010). In addition to that, it was reported by Tan and colleagues (2011) that BV2 microglia pre-treated with δ-tocotrienol showed highest reduction in NO production compared to treatment with the α-and γ-isomers. These findings raised the current interest in investigating whether δ-tocotrienol could result in down-regulation of the microglial inflammatory responses.

The immunoregulatory effects of δ-tocotrienol in inhibiting microglial activation were further explored in the current study. In order to study the protective effects of δ-tocotrienol on microglial inflammatory responses, microglia were pre-treated with δ-tocotrienol for 24 hrs prior to stimulation into an inflammatory phenotype. Five different concentrations of δ-tocotrienol, namely 10, 12.5, 15, 17.5 and 20 μg/mL, were screened for their ability to reduce NO production by primary microglia. Following the previous finding which showcased 20 μg/mL of δ-tocotrienol being the best concentration in reducing NO production in BV2 microglia cell line (Tan *et al.*, 2011), the current study investigated whether this concentration (together with four newly tested concentrations) of δ-tocotrienol could offer similar down-regulatory effects in primary microglial cells. The two most effective concentrations of δ-tocotrienol in NO reduction were selected for downstream experiments. Inflammatory cytokine production (TNF-α, IL-1β, IL-6 and IL-10), eicosanoid biosynthesis (COX-1, COX-2, 5-LOX, PGE2, LTB4) and co-stimulatory molecule CD40 expression in microglia were determined. Moreover, as previous works have revealed the ability of tocotrienols to inhibit NO production (Tan *et al.*, 2011), the mechanism of this inhibition

was examined by determining whether it involved nitrite scavenging or reduced iNOS enzyme expression. Lastly, high-performance liquid chromatography (HPLC) was performed to determine the cellular uptake of δ-tocotrienol by BV2 microglia. This work expands the current knowledge on potential immunomodulatory effects of tocotrienols on microglial responses.

General Objective

The general objective of this project is to determine the effect of pre-treatment with palm δ-tocotrienol on the inflammatory phenotype of microglia.

Specific objectives:

1. to characterise the effect of palm δ-tocotrienol on the inflammatory phenotype of microglia including the production of pro-inflammatory cytokines, eicosanoids as well as expression of CD40 co-stimulatory molecule.
2. to determine the mechanism involved in the inhibition of microglial nitric oxide (NO) expression by palm δ-tocotrienol.
3. to examine the kinetics of palm δ-tocotrienol incorporation into microglia and its retention after 24 hrs.

General Hypothesis

Palm δ-tocotrienol reduces microglia inflammatory responses by reducing the expression of inflammatory mediators and microglial co-stimulatory molecule, CD40.

Specific Hypotheses

1. Palm δ-tocotrienol limits microglial NO production by inhibiting the expression of inducible nitric oxide synthase (iNOS) expression.

2. Palm δ-tocotrienol decreases the production of pro-inflammatoy cytokines and eicosanoids as well as expression of CD40 co-stimulatory molecule in microglia to render activated-microglia less inflammatory.

3. Palm δ-tocotrienol is incorporated into the microglia as soon as administration begins and is retained in the microglia 24 hours later.

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LIST OF PUBLICATIONS

Full Papers

Tan SW, Abdullah M, Ali DAI & Vidyadaran S. (2016). Palm tocotrienols reduce lipopolysaccharide-stimulated inflammatory responses of microglia. *Malaysian Journal of Medicine and Health Sciences* **12,** 1-7.

Jose S, **Tan SW**, Tong CK & Vidyadaran S. (2015). Isolation and characterization of primary microglia from post-natal murine brain tissues: a comparison of two methods. *Cell Biology International* **39,** 1355-1363.

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Proceedings

1. **Tan SW** & Vidyadaran S. δ-Tocotrienol Action on Microglia Responses (2014). Malaysian Journal of Pathology 36(3): 223 – 242.

2. **Tan SW**, Ahmad Israf Ali D, Khaza'Ai H and Vidyadaran S (2016). Anti- inflammatory effects of palm δ- tocotrienol on LPS/IFN- γ- stimulated microglia. Front. Cell. Neurosci. Conference Abstract: 14th Meeting of the Asian- Pacific Society for Neurochemistry. doi: 10.3389/conf.fncel.2016.36.00178.

Posters

1. **Shi Wei Tan**, Wong Jia Woei, Huzwah Khaza'ai, Daud Ahmad Israf Ali and Sharmili Vidyadaran. Anti-inflammatory action of palm δ-tocotrienol on microglia. Palm International Nutra-Cosmeceutical Conference 2017 (PINC 2017). Le Meridien Putrajaya. 31st July- 1st August 2017.

2. **Shi Wei Tan**, Daud Ahmad Israf Ali, Huzwah Khaza'Ai and Sharmili Vidyadaran. Anti- inflammatory effects of palm δ-tocotrienol on LPS/IFN- γ- stimulated microglia. 14th Meeting of the Asian-Pacific Society for Neurochemistry (APSN 2016). Hotel Istana Kuala Lumpur. 27th-30th August 2016.

3. **Shi Wei Tan** and Sharmili Vidyadaran. δ-Tocotrienol Action on Microglia Responses. Immunology Symposium 2014. Faculty of Medicine and Health Sciences, Universiti Putra Malaysia. 16th-17th October 2014.

4. **Shi Wei Tan** and Sharmili Vidyadaran. Tocotrienol Action on Microglia Responses. 3rd International NeuroMalaysia Symposium 2012. Monash University Malaysia. 29th-30th November 2012.

Awards

1. Bursary to attend to 3rd IBRO School of Neuroscience, Monash University Sunway Campus, Malaysia from International Brain Research Organization (IBRO). Year 2012.

2. Best Poster Presenter, 3rd International NeuroMalaysia Symposium, Monash University Sunway Campus from NeuroMalaysia Society. Year 2012.

3. Gift Her with Life Education Grant Recipient from Miss Malaysia India Care Association (MMICARE). Year 2012.

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