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CARDAMONIN FROM Alpinia rafflesiana WALL. EX BAKER AS INHIBITOR OF INFLAMMATORY RESPONSES IN IFN-GAMMA/LPS-STIMULATED MICROGLIAL CELL LINE (BV2) VIA NF-κB SIGNALLING PATHWAY

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By

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CARDAMONIN FROM *Alpinia rafflesiana* WALL. EX BAKER AS INHIBITOR OF INFLAMMATORY RESPONSES IN IFN-GAMMA/LPS-STIMULATED MICROGLIAL CELL LINE (BV2) VIA NF-κB SIGNALLING PATHWAY

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Chairman: Syahida Ahmad, PhD

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The prevalence of neurodegenerative diseases affecting the worldwide population is showing an elevating trend over the last two decades. Chronic neuroinflammation has been proven to contribute to the pathogenesis of these diseases and over-activated microglial cells as well as the inflammatory mediators produced play a crucial role in sustaining the progression of neuroinflammation. In the anti-inflammatory approach, non-steroidal anti-inflammatory drugs (NSAIDs) are among the therapeutic choices and are anticipated to be useful drugs in treating neuroinflammation. Unfortunately, NSAIDs-associated adverse effects had hampered the long term usage of these drugs and thus prompted the investigations for discovering innovative therapeutics for neurodegenerative diseases. Previously, cardamonin isolated from *Alpinia rafflesiana* was shown to possess promising anti-inflammatory property in macrophages and hence potential to be used as a therapeutic agent for various inflammatory diseases. However, the mechanism of action and molecular basis of cardamonin on microglial cells, which are the central

nervous system (CNS)-specific macrophages, still remains unknown. Hence, the main objectives of this study were to investigate the effects of cardamonin on microglial inflammatory responses as well as its mechanism of action in cellular model of neuroinflammation.

In this study, effects of cardamonin on nitric oxide (NO) production in recombinant mouse interferon-γ (IFN-γ) and *Escherichia coli* lipopolysaccharide (LPS)-stimulated microglial cell line (BV2) were evaluated using Griess assay while immunoassays were used for determination of prostaglandin E_2 (PGE_2), tumour necrosis factor-α (TNF-α), interleukin-1β (IL-1β) and interleukin-6 (IL-6) secretion. To decipher the mechanism in which cardamonin possibly regulates microglia, effects of cardamonin on inducible nitric oxide synthase (iNOS) and cyclooxygenases (COX) protein expression as well as the gene expression of TNF-α, IL-1β and IL-6 were determined. In order to understand the effects of cardamonin on cell signal transduction, NF-κB DNA binding activity as well as cell surface expression of cluster of differentiation 14 (CD14) and toll-like receptor 4 (TLR4) of cardamonin-treated BV2 cells were investigated.

Results obtained demonstrated that cardamonin inhibited NO and PGE_2 production in IFN-γ/LPS-stimulated BV2 cells dose-dependently, with IC_{50} values of 27.45 ± 0.46 μM and 2.52 ± 0.12 μM, respectively. This inhibitory effect was contributed by the suppression of cardamonin on the protein expression of iNOS and COX-2, respectively, without affecting COX-1 protein expression. Besides, cardamonin also reduced the production of TNF-α, IL-1β and IL-6 with the IC_{50} values of 40.02 ± 4.01 μM, 5.25 ± 0.85 μM and 13.36 ± 1.52 μM, respectively as well as inhibited the

gene expression of these three cytokines. The results further verified the interruption of cardamonin on NF-κB signalling pathway by attenuation of NF-κB DNA binding activity. Interestingly, cardamonin was found to demonstrate suppressive effect on the cell surface expression of CD14 in IFN-γ/LPS-stimulated BV2 cells as well.

In conclusion, these experimental data have provided mechanistic insights for the anti-inflammatory actions of cardamonin on BV2 cells via suppression of CD14 signalling followed by interruption of NF-κB activation. With these results, it could be projected that by limiting the inflammatory responses of microglia, the tissue injury and neuron death associated with neuroinflammatory diseases may be lessened by cardamonin. Thus, cardamonin could be a potential lead compound for developing anti-inflammatory drugs for neuroinflammatory diseases.

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

CARDAMONIN DIPENCILKAN DARIPADA *Alpinia rafflesiana* WALL. EX BAKER SEBAGAI PERENCAT UNTUK TINDAK BALAS KERADANGAN PADA SEL MIKROGLIA (BV2) YANG DIRANGSANG OLEH IFN-γ/LPS MELALUI TRANSDUKSI ISYARAT NF-κB

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Kelaziman penyakit kemerosotan sistem saraf yang mempengaruhi populasi sedunia menunjukkan peningkatan sejak dua dekad yang lepas. Keradangan sistem saraf kronik telah dibuktikan menyumbang kepada patogenesis penyakit ini. Sel mikroglia yang terlampau aktif dan penghasilan bahan perantaraan keradangan memainkan peranan yang kritikal dalam keradangan sistem saraf yang berterusan. Ubat anti-keradangan tanpa steroid merupakan antara pilihan rawatan dan dijangka berguna untuk merawat keradangan sistem saraf. Malangnya, kesan sampingan yang melibatkan penggunaan ubat anti-keradangan tanpa steroid ini telah menghalang penggunaan jangka masa panjang ubat ini dan menggesa penyelidikan ke arah penemuan rawatan inovatif untuk penyakit kemerosotan sistem saraf. Sebelum ini, cardamonin yang dipencilkan daripada *Alpinia rafflesiana* telah dibuktikan memiliki kesan anti-keradangan pada sel makrofaj dan dengan ini berpotensi untuk dijadikan sebagai ejen terapeutik untuk pelbagai penyakit keradangan. Walau bagaimanapun, mekanisme tindak balas dan asas molekul cardamonin pada sel mikroglia yang

merupakan makrofaj spesifik dalam sistem saraf pusat, masih tidak diketahui lagi. Oleh itu, objektif utama kajian ini adalah untuk mengkaji kesan cardamonin pada tindak balas keradangan mikroglia dan mekanisme tindak balasnya dalam model selular keradangan sistem saraf.

Dalam kajian ini, kesan cardamonin pada penghasilan nitrik oksida (NO) dalam sel mikroglia (BV2) yang dirangsang dengan interferon-γ (IFN-γ) dan LPS *Escherichia coli* telah dinilai menggunakan ujian Griess manakala ujian imuno digunakan untuk menentukan perembesan PGE_2, TNF-α, IL-1β dan IL-6. Untuk mentafsir mekanisme yang mungkin digunakan oleh cardamonin untuk mengawal atur mikroglia, kesan cardamonin ke atas ekspresi protein iNOS yang boleh diaruh dan COX serta ekspresi gen TNF-α, IL-1β dan IL-6 telah dikenal pasti. Untuk memahami kesan cardamonin pada transduksi isyarat, percantuman NF-κB DNA serta ekspresi CD14 dan TLR4 pada permukaan sel mikroglia BV2 telah dikaji.

Daripada kajian yang telah dijalankan, didapati cardamonin merencat pengeluaran NO dan PGE_2 dari sel BV2 yang dirangsang dengan IFN-γ/LPS dengan nilai IC_{50} 27.45 ± 0.46 μM and 2.52 ± 0.12 μM, masing-masing. Kesan perencatan ini adalah disebabkan oleh kesan perencatan ekspresi protein iNOS dan COX-2, tanpa mempengaruhi ekspresi protein COX-1. Selain itu, cardamonin juga mengurangkan penghasilan TNF-α, IL-1β dan IL-6 masing-masing dengan nilai IC_{50} 40.02 ± 4.01 μM, 5.25 ± 0.85 μM and 13.36 ± 1.52 μM, disertai dengan perencatan ekspresi gen ketiga-tiga sitokin ini. Kajian ini mengesahkan kesan perencatan cardamonin ke atas transduksi isyarat NF-κB dengan merencatkan percantuman NF-κB dan DNA. Lebih

menarik lagi, cardamonin juga dapat merencatkan ekspresi CD14 pada permukaan sel BV2 yang dirangsang dengan IFN-γ/LPS.

Kesimpulannya, kajian ini telah memberikan kefahaman mekanisma anti-keradangan cardamonin pada sel BV2 melalui perencatan isyarat CD14 diikuti dengan perencatan pengaktifan NF-κB. Dengan penemuan ini, malah boleh ditunjukkan bahawa, dengan mengehadkan tindak balas keradangan mikroglia, kecederaan tisu dan kematian neuron berkaitan dengan penyakit keradangan sistem saraf dapat dikurangkan dengan cardamonin. Oleh itu, cardamonin berpotensi untuk dijadikan sebagai bahan sebatian kimia utama bagi penemuan dadah anti-keradangan untuk penyakit keradangan sistem saraf.

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I certify that a Thesis Examination Committee has met on 20 April 2012 to conduct the final examination of Chow Yuh Lit on her thesis entitled "Cardamonin from *Alpinia rafflesiana* Wall. ex Baker as inhibitor of inflammatory responses in IFN-gamma/LPS-stimulated microglial cell line (BV2) via NF-κB signalling pathway" in accordance with 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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This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Master of Science. The members of the Supervisory Committee were as follow:

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DECLARATION

I declare that the thesis is my original work except for quotations and citations, which have been duly acknowledged. I also declare that it has not been previously, and is not concurrently, submitted for any other degree at Universiti Putra Malaysia or any institutions.

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CHOW YUH LIT

20 April 2012

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LIST OF ABBREVIATIONS

Aβ	Amyloid-beta peptide
AD	Alzheimer's disease
ALS	Amyotrophic lateral sclerosis
APP	Amyloid presursor protein
CD14	Cluster of differentiation 14
CNS	Central nervous system
COX	Cyclooxygenase
CSF	Cerebrospinal fluid
Da	Dalton
DMEM	Dulbecco's Modified Eagle Medium
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
eNOS	Endothelial Nitric Oxide Synthase
EDTA	Ethylenediaminetetraacetic acid
ELISA	Enzyme-linked Immunosorbent Assays
EMSA	Electrophoretic mobility shift assay
FITC	Fluorescein isothiocyanate
FW	Formula weight
GAPDH	Glyceraldehyde 3‑phosphate dehydrogenase
HD	Huntington's disease
h	hour/s
HRP	horseradish peroxidase
IC_{50}	Inhibitory concentration 50%

IFN-γ	Interferon gamma
IgG	Immunoglobulin
IL	Interleukin
iNOS	Inducible nitric oxide synthase
L	Litre
L-NAME	Nϖ-nitro-L-arginine methyl ester
LPS	Lipopolysaccharide
µg	Microgram
µL	Microlitre
µM	Micromolar
mg	Milligram
min	Minute
mL	Millilitre
mM	Millimolar
mRNA	Messenger ribonucleic acid
MHC	Major histocompatibility complex
MS	Multiple sclerosis
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide
NF-κB	Nuclear factor-kappa B
ng	Nanogram
nm	Nanometer
nNOS	Neuronal Nitric Oxide Synthase
NMR	Nuclear Magnetic Resonance
NO	Nitric oxide
NO_2^-	Nitrite

NSAIDs	Non-steroidal anti-inflammatory drugs
ºC	Degree celcius
PBS	Phosphate buffer saline
pg	Picogram
PD	Parkinson's disease
PGE_2	Prostaglandin E_2
rpm	Rotation per minute
RT-PCR	Reverse transcription polymerase chain reaction
SDS-PAGE	Sodium dodecyl sulphate-polyacrylamide gel electrophoresis
SEM	Standard error of the mean
TLR4	Toll-like receptor 4
TNF	Tumour necrosis factor
U	Unit
xg	Gravities (Unit for relative centrifugal force)

CHAPTER 1

INTRODUCTION

Advancement in medical and pharmacological development had triumphantly increased the average life span of human population globally. However, parallel with this increment in life expectancy, more people are living long enough to suffer from age-related loss of function and disease including neurodegenerative disorders, such as Alzheimer's disease (AD), Parkinson's disease (PD) and amyotrophic lateral sclerosis (Matteo and Esposito, 2003). Apart from aging, genetic and environmental factors are other important causative agents for neurodegenerative diseases namely, Huntington's disease (HD) (Roos, 2010) and multiple sclerosis (MS) (Hemmer *et al.*, 2006). To date, an ideal therapy without long term debilitating side effects for these neurodegenerative diseases is still under the pursue of neuroscientists due to the diverse etiology of the disorders. Fortunately, despite the multiple risk factors for the pathogenesis of these central nervous system (CNS) degenerating disorders, a handful of evidences have identified chronic neuroinflammation as the convergence point of the disease pathologies as reviewed by Tansey and Goldberg (2010), Frank-Cannon *et al.* (2009) as well as Block and Hong (2005).

In the course of chronic neuroinflammation, microglia which is the resident immune cell of the CNS, plays a crucial role. Unlike the activated microglia found in acute neuroinflammation which are neuroprotective, this prolonged, over-activation of microglia results in the release of a myriad of inflammatory mediators which are neurotoxic (Tambuyzer *et al.*, 2009; Block and Hong, 2005; Aloisi, 2001). Nitric oxide (NO) is a free radical produced by inducible nitric oxide synthase (iNOS) and

it is prominently expressed in activated microglia in response to immunologic challenges such as lipopolysaccharide (LPS), interferon-γ (IFN-γ), tumour necrosis factor-α (TNF-α) and interleukin (IL)-1β (Vincent, 1994; Nathan, 1992). NO produced as well as its derivatives including reactive nitrogen oxides and superoxide anions could mediate neurotoxicity and contribute to the progression of neurodegenerative diseases such as in AD (Liu *et al.,* 2002) and PD (Iravani *et al.,* 2001).

In addition to iNOS, cyclooxygenase-2 (COX-2) is another inducible protein in which its expression is highly elevated in activated microglia. Following the increased expression of COX-2, a surge is observed in the production of prostaglandin E_2 (PGE_2), which is the main inflammatory product of this protein (Minghetti and Levi, 1998). Along with microglial over-activation, a variety of inflammatory cytokines namely TNF-α, IL-1β and IL-6 are being secreted in large amount as well (McCarty, 2006; Owens *et al.,* 2005). These inflammatory mediators work in concert to exacerbate the chronically sustained, unmitigated inflammatory episodes in the CNS and eventually contribute to the degenerative insults (Hensley, 2010). Hence, by reducing the expression of these mediators, their detrimental effects contributing to neuronal cell death could be largely eliminated.

Ever since the involvement of neuroinflammation in the pathogenesis of neurodegenerative disorders had been unraveled, research on non-steroidal anti-inflammatory drugs (NSAIDs) had developed and the neuroprotective effect resulted from the suppression of inflammatory responses shown by long term NSAIDs use were observed in several neurodegenerative disease models such as AD (Dokmeci,

2004; Halliday *et al.*, 2000; Beard *et al.*, 1998; Andersen *et al.*, 1995) and PD (Becker *et al.*, 2011). Unfortunately, adverse effects including gastrointestinal complications (Beppu *et al.*, 2011; Bidaut-Russell and Gabriel; 2001; Buttgereit *et al.*, 2001), cardiovascular risks (Krotz and Struthmann, 2010; Motsko *et al.*, 2006) and nephrotoxicity (Harirforoosh and Jamali, 2009) which occurred following the consumption of NSAIDs had hampered the long-term usage of these drugs. As a consequence, the discovery of alternative anti-inflammatory drugs or treatments is of utmost importance.

On the natural end of the treatment spectrum, a wide variety of phytochemicals possessing anti-inflammatory property are potential compounds for developing anti-inflammatory drugs in treating neuroinflammation (Lu *et al.*, 2010; Ha *et al.*, 2008; Hwang *et al.*, 2008; Lim *et al.*, 2008; Jung *et al.*, 2007; Moon *et al.*, 2007). Cardamonin isolated from *Alpinia rafflesiana* is one of the naturally occurring chalcone which showed promising anti-inflammatory effects on macrophages (Syahida *et al.*, 2006) through the inhibition of nuclear factor-kappa B (NF-κB) signalling pathway (Israf *et al.*, 2007).

In this study, the effects of cardamonin on chronic neuroinflammatory responses and the possible mechanisms of action were explored and elucidated by using a cellular model of neuroinflammation. First, murine microglial cell line (BV2) were stimulated with recombinant mouse interferon-γ (IFN-γ) and *Escherichia coli* lipopolysaccharide (LPS), followed by cardamonin treatment. The effects of cardamonin on IFN-γ/LPS-stimulated BV2 cells were then determined by various downstream experiments, including assaying inflammatory mediators (NO, PGE_2

and cytokines) production, iNOS and COX protein production, cytokines gene expression, NF-κB DNA binding activity as well as cell surface expression of cluster of differentiation 14 (CD14) and toll-like receptor 4 (TLR4).

The hypothesis of this study states that cardamonin from *Alpinia rafflesiana* might be able to suppress inflammatory responses in this cellular model of neuroinflammation by inhibiting NF-κB signalling pathway and cell surface expression of LPS receptors (CD14 and TLR4).

Objectives of the study

The general objective of this project is to elucidate the possible anti-inflammatory properties of cardamonin from *Alpinia rafflesiana* on IFN-γ/LPS-stimulated BV2 microglial cell line.

The specific objectives are:

1. To evaluate the effects of cardamonin on iNOS protein expression and NO production in IFN-γ/LPS-stimulated BV2 cells.
2. To examine the effects of cardamonin on protein expression of COX-1 and COX-2 as well as the secretion of PGE_2 in IFN-γ/LPS-stimulated BV2 cells.
3. To investigate the effects of cardamonin on both the production and gene expression of TNF-α, IL-1β and IL-6 in IFN-γ/LPS-stimulated BV2 cells.
4. To understand the effects of cardamonin on NF-κB DNA binding activity in IFN-γ/LPS-stimulated BV2 cells.
5. To ascertain the effects of cardamonin on CD14 and TLR4 cell surface expression in IFN-γ/LPS-stimulated BV2 cells.

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BIODATA OF STUDENT

The author, Chow Yuh Lit was borned in 1986 at Klang, Selangor, Malaysia. She received her early education at Sekolah Jenis Kebangsaan (Cina) Choong Hua, Banting, Selangor and then went to Sekolah Menengah Kebangsaan Telok Datok, Selangor for secondary education. After completed SPM examination, she entered matriculation at Kolej Matrikulasi Negeri Sembilan before furthering her study at tertiary level in Universiti Putra Malaysia (UPM) and graduated with B.Sc. (Biotechnology) in year 2008. In August 2009, she was offered scholarship (Graduate Research Fellowship) by UPM to pursue her Master's degree at Institute of Bioscience (IBS), UPM under the supervision of Dr. Syahida Ahmad. During her postgraduate study, the author has been awarded with Neuroscience Student Award in the 2nd Annual Neuroscience Seminar 2011 jointly organized by Faculty of Medicine and Health Sciences (UPM), Malaysian Society of Neurosciences and NeuroMalaysia Society.

PUBLICATIONS

Poster Presentation

1. **Chow, Y.L.**, Vidyadaran, S., Lajis, N.A., Syahida, A. Effects of Cardamonin on Pro-inflammatory Mediators Production in LPS/IFN-γ-Stimulated Murine Microglial Cell Line BV2. International Anatomical Sciences and Cell Biology Conference in National University of Singapore, Singapore, 26th - 29th May 2010.

Oral Presentation

1. **Chow, Y.L.**, Vidyadaran, S., Lajis, N.A., Syahida, A. Cardamonin from *Alpinia rafflesiana* Inhibits Inflammatory Responses in IFN-γ/LPS-Stimulated Cell Line BV2 via NF-κB Signalling Pathway. 2nd Annual Neuroscience Seminar 2011 in Universiti Putra Malaysia, 23rd June 2011.

Full Paper

1. **Chow, Y.L.**, Lee, K.H., Vidyadaran, S., Israf, D.A., Lajis, N.H., Akhtar, M.N. and Syahida, A. Cardamonin from *Alpinia rafflesiana* inhibits inflammatory responses in IFN-γ/LPS-stimulated BV2 microglia via NF-κB signalling pathway. *International Immunopharmacology*. DOI information: 10.1016/j.intimp.2012.01.009 (Article accepted for publication on 20 Jan 2012).

Award

1. **Neuroscience Student Award (2011)**

   Cardamonin from *Alpinia rafflesiana* Inhibits Inflammatory Responses in IFN-γ/LPS-Stimulated Cell Line BV2 via NF-κB Signalling Pathway. 2nd Annual Neuroscience Seminar 2011 in Universiti Putra Malaysia, 23rd June 2011.