EFFECTS OF SYNTHESIZED CURCUMIN DERIVATIVES (MS65) ON INTERLEUKIN-6 AND ITS SIGNALLING PATHWAYS IN HISTAMINE-INDUCED KERATINOCYTES CELL LINE

NURUL ATIKA BINTI RAZALI

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By

NURUL ATIKA BINTI RAZALI

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Chairman : Associate Professor Syahida Ahmad, PhD
Faculty : Biotechnology and Biomolecular Sciences

Allergic skin diseases are the most common dermatological problems with a dramatic increase in prevalence over the last few decades. Histamine is a well-known chemical mediator that is involved in allergic inflammation and immune modulation by regulating numerous cellular functions via up-regulation of proinflammatory cytokines. In recent years, antihistamines remain the mainstay of allergy treatment by suppressing the transcription of inflammatory cytokines, chemokines and adhesion molecules. However, current usage of antihistamines is limited in efficacy and associated with several common side effects. Currently, alternative therapeutic preferences are derived from natural products in an effort to provide safer and more reliable anti-inflammatory agents. Chalcone, curcumin and their derivatives are among compounds of interest in natural product research due to numerous pharmacological benefits including anti-inflammatory activities. Therefore, the aim of this study was to investigate the effects of synthesized compounds consisting of chalcone and curcumin derivatives in reducing cytokine production in human keratinocytes upon stimulation with histamine, a potent mediator of allergic responses. In the present study, IL-1β and IL-6 cytokine production in histamine-induced human keratinocytes cell line (HaCaT) were measured using ELISA and cytotoxicity effects were determined using MTT assay. Histamine (10 µM) enhances the production of IL-1β and IL-6 in HaCaT cells, with the highest production of IL-1β and IL-6 at 2.67 ± 0.43 pg/mL and 97.41 ± 2.33 pg/mL respectively after 24 h of exposure. Four chemically synthesized compounds consisting of chalcone derivatives (FLA and FLB) and curcumin derivatives (BDMC33 and MS65) were then evaluated for their inhibitory effects on IL-6 production in histamine-induced HaCaT cells. Out of the four compounds tested, the curcumin derivative (MS65) demonstrated a promising anti-inflammatory activity by inhibiting IL-6 production with IC_{50} value of 4.91 ± 2.50 µM with low cytotoxicity effect to HaCaT cell and LC_{50} value of 28.82 ± 7.56 µM. MS65 has shown to inhibit IL-6 through NF-κB and MAPK pathways by suppressing

H1R, *PKC*, *IKK-α, IκB-β, NF-κB, c-Raf*, *MEK* and *ERK* genes. MS65 showed the highest inhibition on *H1R* gene by 5-fold (0.23 ± 0.02 fold expression) at the concentration of 6.25 µM. The present study has provided mechanistic insights into the ability of MS65 to reduce inflammatory cytokine production stimulated by histamine in human keratinocytes via inhibition of NF-κB and MAPK pathways. These findings suggest that the curcumin derivative, MS65 could be used as a lead compound on developing new medicinal agent for the treatment of allergic skin diseases.

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

KESAN KURKUMIN DERIVATIF SINTETIK TERHADAP INTERLEUKIN-6 DAN ISYARAT TAPAK JALANNYA DALAM SEL KERATINOSIT YANG DIRANGSANG OLEH HISTAMIN

Oleh

NURUL ATIKA BINTI RAZALI

April 2017

Pengerusi : Profesor Madya Syahida Ahmad, PhD
Fakulti : Bioteknologi dan Sains Biomolekul

Penyakit kulit disebabkan oleh alahan merupakan masalah dermatologi biasa dengan peningkatan dramatik sejak beberapa dekad yang lalu. Histamin ialah pengantara kimia terkenal yang terlibat dalam keradangan alahan dan modulasi imun dengan mengawal pelbagai fungsi selular melalui pengeluaran sitokin yang tinggi. Beberapa tahun kebelakangan ini, antihistamin masih menjadi rawatan utama bagi alahan dengan menghalang pengeluaran sitokin, kemokin dan molekul adhesif. Walau bagaimanapun, keberkesanan penggunaan antihistamin bagi rawatan penyakit alahan adalah terhad dan dikaitkan dengan beberapa kesan sampingan. Sejak akhir-akhir ini, beberapa alternatif terapeutik telah diperolehi daripada produk semula jadi dalam usaha untuk menyediakan ejen anti-radang yang lebih selamat dan lebih dipercayai. Kalkon, kurkumin dan derivatifnya adalah antara sebatian penting dalam penyelidikan produk semulajadi kerana mempunyai pelbagai manfaat farmakologi termasuklah aktiviti anti-radang. Oleh itu, kajian ini bertujuan untuk mengkaji kesan sebatian sintetik yang terdiri daripada kalkon dan kurkumin derivatif dalam mengurangkan pengeluaran sitokin pada keratinosit manusia yang dirangsang oleh histamin, pengantara utama bagi proses alahan. Dalam kajian ini, pengeluaran sitokin IL-1β dan IL-6 dalam sel keratinosit manusia (HaCaT) yang dirangsang histamin diukur menggunakan ELISA manakala kesan sitotoksik histamin dikaji menggunakan asai MTT. Histamin (10 µM) didapati dapat meningkatkan pengeluaran IL-1β dan IL-6 dalam sel HaCaT dengan pengeluaran tertinggi IL-1β dan IL-6 iaitu sebanyak 2.67 ± 0.43 pg/mL dan 97.41 ± 2.33 pg/mL selepas 24 jam pendedahan histamin. Empat sebatian sintetik terdiri daripada kalkon derivatif (FLA dan FLB) dan kurkumin derivatif (BDMC33 dan MS65) kemudiannya dinilai untuk kesan pengurangan terhadap pengeluaran IL-6 dalam sel HaCaT yang dirangsang histamin. Daripada empat sebatian yang diuji, kurkumin derivatif (MS65) menunjukkan aktiviti anti-radang terbaik dalam pengurangan pengeluaran IL-6 dengan nilai IC_{50} sebanyak 4.91 ± 2.50 µM kurang toksik kepada sel HaCaT dengan nilai LC_{50} sebanyak 28.82 ± 7.56

μM. MS65 menghalang tapak jalan NF-κB dan MAPK dengan menyekat gen *H1R*, *PKC*, *IKK-α, IκB-β, NF-κB, c-Raf*, *MEK* dan *ERK*. MS65 menunjukkan penyekatan tertinggi terhadap gen H1R dengan lima kali ganda (0.23 ± 0.02 kali ganda ekspresi) pada kepekatan 6.25 μM. Hasil kajian ini telah memberikan pandangan mekanistik terhadap kebolehan MS65 untuk mengurangkan pengeluaran sitokin yang dirangsang oleh histamin dalam keratinosit manusia melalui penghalangan tapak jalan NF-κB dan MAPK. Penemuan ini mencadangkan bahawa kurkumin derivatif, MS65 boleh digunakan sebagai sebatian utama dalam penghasilan ejen ubatan baru bagi rawatan penyakit kulit alahan.

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This thesis was submitted to the Senate of the 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:

Syahida Ahmad, PhD
Associate Professor
Faculty of Biotechnology and Biomolecular Sciences
Universiti Putra Malaysia
(Chairman)

Lai Kok Song, PhD
Senior Lecturer
Faculty of Biotechnology and Biomolecular Sciences
Universiti Putra Malaysia
(Member)

Faridah Abas, PhD
Associate Professor
Faculty of Food Science and Technology
Universiti Putra Malaysia
(Member)

ROBIAH BINTI YUNUS, PhD
Professor and Dean
School of Graduate Studies
Universiti Putra Malaysia

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Signature:	_____
Name of Member of Supervisory Committee:	Dr. Lai Kok Song
Signature:	_____
Name of Member of Supervisory Committee:	Associate Professor Dr. Faridah Abas

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LIST OF ABBREVIATIONS

AD	Atopic dermatitis
ALS	Amyotrophic lateral sclerosis
ANOVA	Analysis of variance
BAFF	B cell-activating factor
BDMC33	2,6-bis(2,5-dimethoxybenzylidene)cyclohexanone
cAMP	Cell adhesion molecule
cDNA	Complementary deoxyribonucleic acid
cGMP	Cyclic guanosine monophosphate
CNTF	Ciliary neurotrophic factor
COX-2	Cyclooxygenase-2
c-Raf	RAF proto-oncogene serine/threonine-protein kinase
CS	Contact hypersensitivity
CSF	Colony-stimulating factor
C_T	Threshold cycle
CT-1	Cardiotrophin-1
DC	Dendritic cell
DMEM	Dulbecco's modified eagle medium
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
dsDNA	Double strand deoxyribonucleic acid
EDTA	Ethylenediaminetetraacetic acid
ELISA	Enzyme-linked immunosorbent assay
ELISPOT	Enzyme-linked immunospot
ERK	Extracellular signal–regulated kinase
ETA	Exfoliative toxin A

FBS	Fetal bovine serum
FLA	1-(2-hydroxy-4,6-dimethoxy-phenyl)-3-(4-methoxy-phenyl)-propenone
FLB	1-(2-Hydroxy-4,6-dimethoxy-phenyl)-3-phenyl-propenone
GAPDH	Glyceraldehyde 3‑phosphate dehydrogenase
GM-CSF	Granulocyte macrophage colony-stimulating factor
gp130	Glycoprotein 130
h	Hour
H1R	Histamine H1 receptor
H2R	Histamine H2 receptor
H3R	Histamine H3 receptor
H4R	Histamine H4 receptor
HaCaT	Human adult low calcium high temperature
HDC	Histidine decarboxylase
IC_{50}	Half-maximal inhibitory concentration
IFN	Interferon
IgE	Immunoglobulin E
iNOS	Nitric oxide synthase
$InsP_3$	Inositol-1,4,5-trisphosphate
IκB	Inhibitor of nuclear factor kappa-B
IKK	Inhibitor of nuclear factor kappa-B kinase
IL	Interleukin
IL-1R	Interleukin-1 receptor
IU	International unit
JNK	c-Jun N-terminal kinases
L	Litre
LAF	Lymphocyte-activating factor

LC_{50}	Half-maximal lethal concentration
LIF	Leukemia inhibitory factor
LPS	Lipopolysaccharide
LT-β	Lymphotoxin-β
µg	Microgram
µL	Microlitre
µM	Micromolar
mg	Milligram
min	Minute/s
mL	Millilitre
mM	Millimolar
MAPK	Mitogen activated protein kinase
MEK	Mitogen-activated protein kinase kinase
mIL-6R	Membrane-bound interleukin-6 receptor
mRNA	Messenger ribonucleic acid
MS65	2,6-bis(2-fluorobenzylidene)cyclohexanone
MTT	3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide
NADH	Nicotinamide adenine dinucleotide
NADPH	Nicotinamide adenine dinucleotide phosphate
NEMO	Nuclear factor kappa-B cells essential modulator
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NHEK	Native human epidermal keratinocytes
NLRP3	NACHT, LRR and PYD domains-containing protein 3
NO	Nitric oxide
NSAID	Nonsteroidal anti-inflammatory drug
NTC	Non-template control

OSM	Oncostatin M
PBMC	Peripheral blood mononuclear cells
PBS	Phosphate buffered saline
PDGF	Platelet-derived growth factor
PGE_2	Prostaglandin E2
PKC	Protein kinase C
PLC	Phospholipase C
RA	Rheumatoid arthritis
RANKL	Receptor activator of nuclear factor kappa-B ligand
RFU	Relative fluorescence unit
RNA	Ribonucleic acid
RT-qPCR	Quantitative real-time polymerase chain reaction
s	Second/s
SAPK	Stress-activated protein kinase
SAR	Structure-activity relationship
S.E.M	Standard error of mean
sIL-6R	Soluble forms interleukin-6 receptor
SLE	Systemic lupus erythematosus
TCCD	2,3,7,8-tetrachlorodibenzo-p-dioxin
Th	T helper
TLRs	Toll-like receptors
TMB	3,3',5,5'-tetramethylbenzidine
TNF	Tumor necrosis factor
*x*g	Gravities (Unit for relative centrifugal force)
ºC	Degree celcius

CHAPTER 1

INTRODUCTION

The prevalence of allergic diseases shows a well-documented increase worldwide with the percentage of 20-30%, particularly in low- and middle-income countries (Pawankar et al., 2011). The complexity and severity of these diseases are continually increasing especially in children and young adults, who are profoundly affected by these trends (Pawankar, 2014). In allergy, an exaggerated inflammatory response against a harmless substance initiates a cascade of cellular and molecular events that affect the skin (dermatitis and urticaria), respiratory tract (rhinitis and asthma) and multiple systems (anaphylaxis) (Dave et al., 2011). Skin conditions are among the most common types of allergy treated by allergists. Most of these diseases are chronic and proliferative with a relapsing-remitting course, in which both genetic and environmental factors play important roles (Fonacier et al., 2010). Patients with skin allergies often face a high burden of suffering due to the tremendous impairment in quality of life, mostly caused by an intense itch and stigmatization. In spite of the great progress made in experimental research in allergology and immunology, there are still a number of challenges in developing curative therapies for these allergic diseases (Ring et al., 2009).

In brief, the allergic cascade causes a widespread of inflammatory and proinflammatory activation, robust cytokine and chemokine production, as well as heterogeneity in immune and endothelial responses, leading to the manifestations of allergic reaction (Canonica and Blaiss, 2011). Histamine, a biological amine, has been identified as a major mediator of inflammation and allergic response that regulates the expression of cytokine, chemokines and cell-adhesion molecules (Bäumer et al., 2013; Fitzsimons et al., 2015). The release of histamine in the skin causes a variety of allergic reactions which include redness, itching as well as wheal and flare due to vasodilation and increase in vascular permeability (Thurmond et al., 2008). The exposure of histamine to keratinocytes, the main cells of epidermis (outermost layer of the skin), lead to the formation of an impaired skin barrier, which initiates the expression of proinflammatory molecules that represents the starting point of primary skin inflammation (Gschwandtner et al., 2013; Albanesi, 2010). Generally, histamine exerts its proinflammatory effects mainly through four different receptors (H1, H2, H3 and H4), but mediated mostly by the activation of H1 receptors (H1Rs) in allergic diseases (Marone et al., 2003). The binding of histamine to the H1R results in phosphorylation of protein kinase C (PKC) and downstream activation of nuclear factor-kappa B (NF-κB) and mitogen activated protein kinase (MAPK) transcription factors, which are associated with regulation of adhesion molecules, chemotaxis, antigen presentation and proinflammatory cytokine production (Dávila et al., 2006; Matsubara et al., 2005).

Considering the roles of H1R in mediating proinflammatory effects of histamine, the therapeutic intervention in allergic disorders has thus commonly focused on developing the antagonists of this receptor (Zappia et al., 2015). H1 antihistamines,

also called H1 antagonists, remain as first-line medications for the treatment of allergic diseases due to their effectiveness in providing symptomatic relief (Motala, 2009). The action of H1 antihistamines are associated with the suppression of cytokines, chemokines and adhesion molecules transcription (Leurs et al., 2002; Matsubara et al., 2005). However, increasing evidence have shown that administration of H1 antihistamines is limited in efficacy and associated with a number of side-effects such as nausea, lightheadedness, drowsiness, headaches, agitation and dry mouth (Gutzmer et al., 2011; Motala, 2009). Thus, the discovery of alternative anti-inflammatory agents that are more effective and safe for treatment of allergic skin disorders is of utmost important.

On natural preference of the treatment, a wide spectrum of phytochemicals and their derivatives have been identified for their potential as anti-inflammatory agents. Chalcone and curcumin, as well as their derivatives have attracted increasing interest due to numerous pharmacological benefits. They have displayed a broad spectrum of many pharmacological activities, including anticancer, antioxidant, anti-inflammatory and antimalarial properties (Lahsasni et al., 2014; Wilken et al., 2011; Kumar et al., 2013). For this reason, the versatility and flexibility for structural modification of natural and synthetic derivatives of chalcone and curcumin have been explored extensively for designing new medicinal agents with improved potency and lesser toxicity (Kumar et al., 2013).

In the present study, the production of cytokines (IL-1β and IL-6) were measured in cultures of human keratinocytes cell line (HaCaT) exposed with histamine. Then, four chemically synthesized compounds consisting of chalcone derivatives (FLA and FLB) and curcumin derivatives (BDMC33 and MS65) were evaluated for their inhibitory activity against cytokine productions in histamine-induced human keratinocytes cell line (HaCaT). The selected derivative was then further tested for its inhibition on gene expression level in NF-κB and MAPK pathways. Hypothetically, the selected derivative that is capable of reducing proinflammatory cytokine in keratinocytes stimulated by histamine could be useful in treating skin allergies.

Objectives of the study

The general objective of this study is to elucidate the inhibitory effects of synthesized compounds of chalcone and curcumin derivatives on IL-1β and IL-6 production in keratinocytes exposed to histamine. The specific objectives are:

1) To measure the production of IL-1β and IL-6 in histamine-induced HaCaT cells.
2) To evaluate the inhibitory effects of chalcone derivatives (FLA and FLB) and curcumin derivatives (BDMC3 and MS65) on selected cytokine production in histamine-induced HaCaT cells.
3) To determine the effects of selected derivative on NF-κB and MAPK inflammatory pathways via gene expression of *H1R, PKC, IKK-β, IκB-α, NF-κβ, c-Raf, MEK* and *ERK* in histamine-induced HaCaT cells.

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