UNIVERSITI PUTRA MALAYSIA

ANTI-INFLAMMATORY ACTIVITY OF 5-(3,4-DIHYDROXYPHENYL)-3-HYDROXY-1-(2-HYDROXYPHENYL)PENTA-2,4-DIEN-1-ONE (SYNTHETIC CURCUMINOID ANALOGUE) IN MICE

NADIA BINTI HISAMUDDIN

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By

NADIA BINTI HISAMUDDIN

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

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Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Master of Science

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Chairman : Wan Mastura Shaik Mohamed Mossadeq, PhD
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The rhizome of *Curcuma longa (C. longa)* plant consists of 3-5% curcuminoids. Curcuminoids comprises of curcumin, demethoxycurcumin and bisdemethoxycurcumin. Among these, curcumin has been reported to be responsible for most of the *C. longa* pharmacological activities. However, the biological activities of curcumin are limited due to its solubility and low bioavailability *in vivo*. Numerous curcuminoid analogues with better bioavailability and solubility were synthesized to overcome these limitations. Novel synthetic curcuminoid analogues such as the 5-(3,4- dihydroxyphenyl)-3-hydroxy-1-(2-hydroxyphenyl)penta-2,4-dien-1-one (abbrev. DHHPD), showed good anti-inflammatory activities *in vitro*. Hence, the current study was conducted to evaluate the anti-inflammatory activity of DHHPD in mice using the carrageenan-induced paw oedema and cotton pellet-induced granuloma tests. Mice that received DHHPD (0.1, 0.3, 1 and 3 mg/kg, intraperitoneal) showed a significant decrease ($p<0.05$) in paw oedema formation from the 2nd hour of induction until the end of the experiment. The inhibition induced by DHHPD at 0.1, 0.3, 1 and 3 mg/kg (intraperitoneal) were 65.4%, 66.9%, 73.8% and 86.9% respectively. In the cotton-pellet induced granuloma test, DHHPD (0.1, 0.3, 1 and 3 mg/kg, intraperitoneal) showed significantly marked reductions ($p<0.001$) in granuloma development by 22.1%, 32.6%, 37.2% and 49.3%, respectively. The possible mechanisms of action involved in DHHPD-induced anti-inflammatory effect were evaluated using histamine-, serotonin-, and bradykinin-induced paw oedema tests. Results showed that DHHPD (0.1, 0.3, 1 and 3 mg/kg, intraperitoneal) caused significant ($p<0.05$) reductions in paw oedema formation induced by the intraplantar administration of histamine (100 µg/paw) from the 10th minute until the 40th minute after induction. DHHPD demonstrated significant reductions in the formation of serotonin-induced (100 µg/paw) paw oedema in the 1st hour and from the 3rd to 5th hour whereas bradykinin-induced (10 nmol/paw) paw oedema was significantly reduced by

DHHPD throughout the experiment (1st to 5th hour). In conclusion, DHHPD exerted anti-inflammatory effects in the rodent models of induced inflammation possibly through the histaminergic, serotonergic and bradykininergic systems.

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

AKTIVITI ANTIRADANG 5-(3,4-DIHYDROXYPHENYL)-3-HYDROXY-1-(2-HYDROXYPHENYL)PENTA-2,4-DIEN-1-ONE (ANALOG CURCUMINOID SINTETIK) DALAM MENCIT

Oleh

NADIA BINTI HISAMUDDIN

April 2019

Pengerusi : Wan Mastura Shaik Mohamed Mossadeq, PhD
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Rimpang tumbuhan *Curcuma longa* (*C. longa*) mengandungi 3-5% curcuminoid. Curcuminoid terdiri daripada curcumin, demethoxycurcumin dan bisdemethoxycurcumin. Di antaranya, curcumin telah dilaporkan bertanggungjawab untuk kebanyakan aktiviti farmakologi *C. longa*. Walau bagaimanapun, aktiviti biologi curcumin terhad disebabkan oleh keterlarutannya dan bioavailabiliti yang rendah secara *in vivo*. Banyak analog curcuminoid dengan bioavailabiliti dan kelarutan yang lebih baik telah disintesis untuk mengatasi pembatasan tersebut. Analog curcuminoid sintetik seperti 5-(3,4-dihydroxyphenyl)-3-hydroxy-1-(2-hydroxyphenyl)penta-2,4-dien-1-one (singkatan, DHHPD), menunjukkan aktiviti antiradang secara *in vitro*. Oleh itu, kajian semasa dijalankan untuk menilai aktiviti antiradang DHHPD pada mencit menggunakan ujian edema tapak kaki yang diaruhkan oleh carrageenan dan granuloma yang diaruhkan oleh pelet kapas. Mencit yang menerima DHHPD (0.1, 0.3, 1 dan 3 mg/kg, intraperitoneal) menunjukkan penurunan ketara ($p < 0.05$) dalam pembentukan edema 2 jam selepas induksi sehingga akhir eksperimen. Perencatan yang disebabkan oleh DHHPD pada 0.1, 0.3, 1 dan 3 mg/kg (intraperitoneal) masing-masing adalah 65.4%, 66.9%, 73.8% dan 86.9%. Dalam ujian granuloma yang diaruh oleh pelet kapas, DHHPD pada 0.1, 0.3, 1 dan 3 mg/kg (intraperitoneal) menunjukkan penurunan ketara ($p<0.001$) dalam pembentukan granuloma sebanyak 22.1%, 32.6%, 37.2% dan 49.3%. Mekanisme tindakan yang mungkin terlibat dalam kesan antiradang yang disebabkan oleh DHHPD telah dikaji menggunakan ujian edema yang disebabkan oleh histamine, serotonin, dan bradykinin. Hasil kajian menunjukkan bahawa DHHPD (0.1, 0.3, 1 dan 3 mg/kg, intraperitoneal) menyebabkan pengurangan edema ($p<0.05$) yang diakibatkan oleh suntikan intraplantar histamine (100 µg /tapak) dari minit ke-10 hingga minit ke-40 selepas induksi. DHHPD menunjukkan pengurangan ketara dalam pembentukan edema tapak kaki disebabkan oleh serotonin (100 µg/tapak)

pada jam pertama dan dari jam ke-3 hingga ke-5, manakala edema kaki yang disebabkan oleh bradykinin (10 nmol/tapak) berkurang dengan ketara sepanjang eksperimen (jam pertama hingga jam ke-5). Sebagai kesimpulan, DHHPD menghasilkan kesan antiradang dalam model keradangan teraruh mencit kemungkinan melalui sistem histaminergik, serotonergik dan bradykininergik.

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Nadia binti Hisamuddin

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

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LIST OF ABBREVIATIONS

ANOVA	Analysis of Variance
ASA	Acetylsalicylic acid
µg	Microgram
µg/paw	Microgram per paw
C. longa	*Curcuma longa*
COX	Cyclooxygenase
DHHPD	5-(3,4-dihydroxyphenyl)-3-hydroxy-1-(2-hydroxyphenyl)penta-2,4-dien-1-one
DMSO	Dimethyl sulfoxide
GI	Gastrointestinal
g	Gram
h	Hour
H_o	Null hypothesis
H_a	Alternative hypothesis
ICR	Institute of Cancer Research
IFN-ɣ	Interferon gamma
i.p.	Intraperitoneal
i.pl.	Intraplantar
IL	Interleukin
LOX	Lipooxygenase
LPS	Lipopolysaccharide
kDa	Kilodalton
mg	Milligram
mg/kg	Milligram per kilogram
min	Minute
ml	Millilitre
ml/kg	Millilitre per kilogram
mm	Millimetre
mmol/L	Millimol per liter
nmol/paw	Nanomol per paw
NO	Nitric oxide
NOS	Nitric oxide synthase
NSAIDs	Non-steroidal anti-inflammatory drugs
^{O}C	Degree Celsius
PG	Prostaglandin
PGI_2	Prostacyclin
S.E.M	Standard error mean
TNF	Tumor necrosis factor
w/v	Weight per volume

CHAPTER 1

INTRODUCTION

1.1 Background of study

Presently, there are a variety of non-steroidal anti-inflammatory drugs (NSAIDs) available commercially such as aspirin, acetaminophen (paracetamol), antipyrine, fenamates, phenacetin, phenylbutazone, indomethacin and naproxen (Sánchez-Borges, 2008). However, anti-inflammatory drugs are often associated with several side effects. Depending on the dose administered, these drugs may cause stomach upset and consumption exceeding the recommended dose can induce prolongation of the birth process (Antonucci et al., 2012; Vostinaru, 2017). Moreover, an overdose of these drugs can cause kidney dysfunction. Therefore, numerous studies on the use of various plant and rhizome extracts as alternatives to anti-inflammatory agents have been conducted in order to produce an alternative drug or agent with fewer side effects. Extracts from various parts of the *Curcuma longa* plant for example, are frequently tested for their pharmacological properties *in vivo* and *in vitro*.

Curcuma longa (*C. longa*) or locally known as 'kunyit', belongs to the Zingiberaceae family and is commonly cultivated in the tropical and subtropical provinces, especially in India, Southeast Asia, and China (Rohman, 2012). Various parts of the *C. longa plant* have been shown to possess anti-microbial, anti-diabetic (Arun & Nalini, 2002), anti-inflammatory (Chainani-wu, 2003), anti-fungal, antioxidant, anti-rheumatic (Aggarwal et al., 2006), anti-angiogenic and anti-cancer (Wilken et al., 2011), and hypocholestraemic (Shrishail et al., 2013) activities. Priyadarsini (2014) reported that the curcuminoid group which has been identified as the main component of the *C. longa* rhizome comprises of curcumin, demethoxycurcumin and bisdemethoxycurcumin. However, curcumin has been acknowledged as the main compound that is responsible for many of the plant's pharmacological activities (Joe et al., 2004).

1.2 Problem statement

Although the anti-inflammatory activities of *C. longa* have been widely investigated through *in vivo* and *in vitro* assays, there is a lack of literature on the anti-inflammatory activities of *C. longa* particularly at the compound level. Curcumin (Figure 1.1), the main bioactive curcuminoid present in *C. longa*, exhibited excellent anti-inflammatory and antinociceptive activities *in vivo* and *in vitro*, but were of limited use as a medicinal agent due to its low bioavailability, poor solubility and, its efficient first pass metabolism in the gut.

Therefore, synthetic curcuminoid analogues with better bioavailability and solubility were synthesized. Previously, Leong et al. (2014) had successfully synthesized a series of diarylpentanoid (curcumin analogue) derivatives; all of which were investigated for their possible anti-inflammatory activity *in vitro*. From the study, Compound 97 which is also known as 5-(3,4-dihydroxyphenyl)-3-hydroxy-1-(2-hydroxyphenyl)penta-2,4-dien-1-one (abbrev. DHHPD) (Figure 1.2) significantly suppressed the production of nitric oxide (NO) in the interferon gamma (IFN-ɣ)/lipopolysaccharide (LPS)-stimulated RAW 264.7 macrophages, and was proposed as the most potent anti-inflammatory agent compared to the other ninety-six compounds synthesized. Moreover, the results of DHHPD activities obtained from the absorption, distribution, metabolism, excretion and toxicological analysis (ADMET) and, toxicity prediction of compounds using computer-aided technology (TOPKAT) published in Leong et al. (2014), showed that DHHPD is non-hepatotoxic, does not show skin-sensitizing or ocular irritating properties, possess good HIA activities and most importantly it is highly soluble in water and has low blood-brain barrier activities, compared to other synthetic curcuminoid analogues.

Therefore, the aim of this study is to evaluate the anti-inflammatory activities of DHHPD as well as to identify its possible mechanism action via the mouse model of induced inflammation.

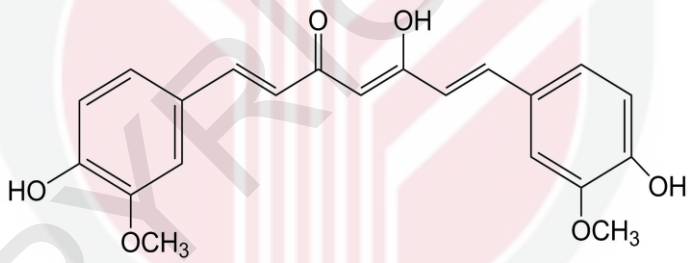

Figure 1.1: The chemical structure of curcumin
(Source: Wilken et al., 2011)

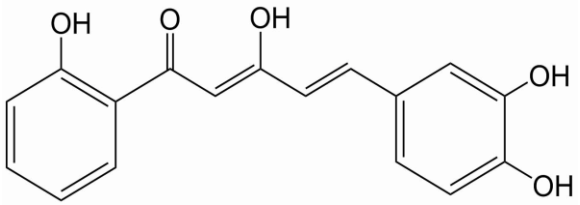

Figure 1.2: The chemical structure of 5-(3,4-dihydroxy phenyl)-3-hydroxy-1-(2-hydroxyphenyl)penta-2,4-dien-1-one
(Source: Leong et al., 2014)

1.3 Significance of study

The findings from this study provide new knowledge on the anti-inflammatory activity of DHHPD, as there is limited scientific information on this subject. In addition, results from the study may be used to support the use of DHHPD-based product as an alternative treatment for inflammation in the future.

1.4 Research objectives

i. To determine the acute toxicity effect of DHHPD in mice
ii. To evaluate the anti-inflammatory activities of DHHPD in mice using the carrageenan induced-paw oedema test and cotton pellet-induced granuloma test
iii. To determine the involvement of the histaminergic, serotonergic and bradykininergic pathways in DHHPD-induced anti-inflammatory activity in mice

1.5 Hyphotheses

i. H_o: DHHPD does not exert toxic effects in mice
   H_a: DHHPD exerts toxic effects in mice

ii. H_o: DHHPD does not produce significant anti-inflammatory activities compared to the control group
   H_a: DHHPD produces significant anti-inflammatory activities compared to the control group

iii. H_o: The histaminergic, serotonergic and bradykininergic systems are not involved in DHHPD-induced anti-inflammatory activities
   H_a: The histaminergic, serotonergic and bradykininergic systems are involved in DHHPD-induced anti-inflammatory activities

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