UNIVERSITI PUTRA MALAYSIA

IN VIVO EVALUATION OF ANTINOCICEPTIVE ACTIVITIES OF 2-BENZOYL-6-(3,4-DIHYDROXYBENZYLIDENE)CYCLOHEXEN-1-OL AND ITS POSSIBLE MECHANISM OF ACTIONS

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By

AHMAD FARHAN BIN AHMAD AZMI

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

September 2021

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

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By

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September 2021

Chair : Mohd Roslan Sulaiman, PhD
Faculty : Medicine and Health Sciences

The present study examined the potential antinociceptive activity of 2-benzoyl-6-(3,4-dihydroxybenzylidene)cyclohexene-1-ol (BDC) and its possible mechanism of actions in mice models. BDC, a novel synthetic curcuminoids was freshly prepared and used throughout this experiment. The experimental models were conducted using 6 male ICR mice per group and the one-way analysis of variance (ANOVA) was used to analysed the gathered data by running Tukey's post hoc test with $p < 0.05$, $p < 0.01$ and $p < 0.001$ for statistically significant different. Based on toxicological studies, BDC showed a Lethal does 50 (LD50) greater than 2000 mg/kg sand categorized 5 according to Globally Harmonized System for the classification of chemicals. The oral administration of BDC at doses of 1-30 mg/kg followed by 7 days consecutive observation did not show any death occurrence or any signs of toxicity. The body weights, liver and kidneys, hematological and liver function parameters showed no sign of abnormality. The findings were further supported by the histopathological observations of the liver, kidney and spleen that demonstrated normal histological structure. The determination of the antinociceptive profiles of BDC were through acetic acid-induced abdominal writhing test and hot plate on mice. BDC shown significant inhibitory activity of pain and prolonged time latency on hot plate, suggesting the possible involvement of BDC in both peripheral and central systems of the pain pathway. The rota-rod evaluation confirmed that the antinociceptive effects of BDC were not associated to any non-specific sedative effects such as muscle relaxant or sedation. Further evaluation with formalin-induced paw licking test demonstrated that BDC interacts with opioid receptors in both phases. The study continued to demonstrate the ability of BDC to inhibit pain through the nitric oxide pathway inactivating a series of event involving the L-Arginine-NO-cGMP-K+-ATP channel pathways in the acetic acid-induced abdominal writhing test. BDC also showed interactions with two other receptors mainly the NMDA and TRPV1 receptors. Moreover, BDC interacts with other

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prominent receptors involved in antinociception including GABAergic, cholinergic, dopaminergic, noradrenergic, serotonergic and adenosinergic systems. The mechanism of action of BDC was further evaluated with the involvement of the Ca2+ activated potassium channels, eventually confirming the involvement of the small and large conductance calcium-gated K+ channels, voltage-gated K+ and ATP-gated K+ channels. The involvement of inflammatory mediators on BDC antinociceptive was evaluated using various inflammatory chemical mediators that act as inducers, mainly bradykinin, histamine, serotonin, substance P, phospholipase A2, prostaglandin E2 and arachidonic acid, of which BDC at all doses significantly suppressed inflammatory mediators-induced inflammation in all inflammatory chemical mediators-induced experiments. As a conclusion, BDC exerted antinociceptive activity by modulating the activation of various receptors, ion channels, L-arginine-nitric oxide-cGMP pathway and descending inhibitory pathways.

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

PENILAIAN *IN VIVO* TERHADAP AKTIVITI ANTINOSISEPTIF 2-BENZOYL-6-(3,4-DIHIDROXYBENZYLIDENE)CYCLOHEXEN-1-OL SECARA DAN KEMUNGKINAN MEKANISMA TINDAKANNYA

Oleh

AHMAD FARHAN BIN AHMAD AZMI

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Pengerusi : Mohd Roslan Sulaiman, PhD
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Kajian ini dijalankan untuk mengenalpasti potensi kesan antinosiseptif 2-benzoyl-6-(3,4-dihydroxybenzylidene)cyclohexene-1-ol (BDC) secara *in vivo* dan kemungkinan mekanisme tindakan terhadap model mencit. BDC merupakan sebatian daripada kurkuminoid sintetik dan telah disediakan dan digunakan sepanjang kajian ini. Model eksperimen telah dijalankan menggunakan 6 tikus ICR jantan bagi setiap kumpulan dan analisis varians sehala (ANOVA) digunakan untuk menganalisis data yang dikumpul melalui ujian post hoc Tukey dengan indikasi $p < 0.05$, $p < 0.01$ dan $p < 0.001$ sebagai statistik yang ketara perbezaannya. Berdasarkan kajian toksikologi, dos maut 50 BDC adalah lebih daripada 2000 mg/kg dan dikategorikan sebagai katogeri 5 mengikut Sistem Harmonis Global bagi klasifikasi bahan kimia. Pemberian BDC melalui mulut pada dos 1-30 mg/kg diikuti oleh 7 hari pemerhatian berturut-turut tidak menunjukkan sebarang kematian atau tanda-tanda keracunan. Berat tubuh, hati, ginjal, parameter hematologi dan fungsi hati tidak menunjukkan tanda-tanda toksik atau kesan sampingan yang bahaya. Penemuan ini telah disokong oleh struktur histologi yang normal berdasarkan pemerhatian histopatologi hati, buah pinggang dan limpa. Kajian kesan antinosiseptif BDC terhadap mencit diteruskan lagi menggunakan ujian pencerutan abdomen daripada aruhan asid asetik dan ujian piring panas. BDC menunjukkan perencatan kesakitan yang ketara dan masa pendam yang lama di atas plat panas, hal ini menunjukkan kemungkinan penglibatan BDC dalam kedua-dua sistem saraf periferi dan sistem saraf pusat. Penilaian rota-rod telah mengesahkan bahawa kesan antinosiseptif BDC tidak melibatkan kesan sedatif yang tidak spesifik seperti kesan penenang otot atau sedasi. Penilaian lanjut melalui ujian jilatan kaki yang diaruh oleh formalin menunjukkan bahawa BDC saling tindak terhadap reseptor opioid pada fasa pertama dan fasa kedua. Kajian ini diteruskan dengan membuktikan keupayaan BDC untuk mengurangkan kesakitan melalui sistem nitrik oksida, dengan penglibatan sistem L-Arginina-NO-cGMP-K+-ATP dalam ujian penggeliatan abdomen daripada aruhan asid

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asetik. BDC juga saling tindak dengan dua reseptor lain terutamanya reseptor NMDA dan TRPV1. Selain itu, BDC juga saling tindak terhadap reseptor-reseptor yang lain termasuk sistem asid gama-aminobutirik, kolinergik, dopaminergik, noradrenergik, serotonergik dan adenosinergik dalam antinosiseptif BDC. Mekanisme tindakan BDC dinilai terhadap saling tindak saluran-saluran ion K+ yang diaktifkan oleh ion Ca2+, dan seterusnya mengesahkan penglibatan saluran K+ kalsium yang beraliran kecil dan besar, saluran voltan K+ dan saluran ATP K+. Kajian penglibatan pengantara inflamasi pada antinosiseptif BDC telah dinilai menggunakan pelbagai pengantara inflamasi sebagai aruhan, terutamanya bradikinin, histamin, serotonin, bahan P, fosfolipase A2, prostaglandin E2 dan asid arakidonik, di mana BDC pada semua dos menunjukkan kesan pengurangan kesakitan yang ketara dalam semua eksperimen yang diaruh oleh pengantara inflamasi. Sebagai kesimpulan, kajian ini telah mengesahkan aktiviti-aktiviti antinosiseptif dan juga mekanisme-mekasnisme tindakan yang terlibat melalui sebatian BDC.

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I certify that a Thesis Examination Committee has met on 21 September 2021 to conduct the final examination of Ahmad Farhan bin Ahmad Azmi on his thesis entitled "*In vivo* Evaluation of 2-Benzoyl-6-(3,4-Dihydroxybenzylidene) Cyclohexene-1-Ol and its Possible Mechanism of Actions" 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 (insert the name of relevant degree).

Members of the Thesis Examination Committee were as follows:

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Declaration by Members of the Supervisory Committee

This is to confirm that:

- the research and the writing of this thesis were done under our supervision;
- supervisory responsibilities as stated in the Universiti Putra Malaysia (Graduate Studies) Rules 2003 (Revision 2015-2016) are adhered to.

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Name of Chairman of Supervisory Committee: Prof. Dr. Mohd Roslan Sulaiman

Signature: _____
Name of Member of Supervisory Committee: Associate Prof. Dr. Enoch Kumar Perimal

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Name of Member of Supervisory Committee: Prof. Dr. Faridah Abas

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LIST OF ABBREVIATIONS

UPM	Universiti Putra Malaysia
DHHPD	5-(3,4-dihydroxyphenyl)-3-hydroxy-1-(2-hydroxyphenyl) penta-2,4-dien-1-one
BHMC	2,6-bis-(4-hydroxyl-3-methoxybenzylidine) cyclohexanone
IFN-ɣ	Interferon gamma
LPS	Lipopolysaccharide
mg/kg	Milligram per kilogram
ml/kg	Milliliter per kilogram
i.p.	Intraperitoneal
i.pl.	Intra plantar
p.o.	Per os
ICR	Institute of cancer research
ANOVA	Analysis of variance
S.E.M.	Standard error mean
IASP	International association for the study of pain
ASA	Acetylsalicylic acid
CAP	Capsazepine
NSAIDs	Non-steroidal anti-inflammatory drugs
CNS	CNS
PNS	Peripheral nervous system
PGE2	Prostaglandin E2
PGE1	Prostaglandin E1
PGA	Prostaglandin A
COX	Cyclooxygenase enzyme
LOX	Lipoxygenase enzyme

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COX1	Cyclooxygenase-1
COX2	Cyclooxygenase-2
TRPA1	Transient receptor potential cation channel subfamily A1
TRPV1	Transient receptor potential vanilloid subtype 1
ATP	Adenosine triphosphate
GABA	γ-Aminobutyric acid
GABAA	γ-Aminobutyric acid type A
GABAB	γ-Aminobutyric acid type B
Ca2+	Calcium ion
Na+	Sodium ion
Cl-	Chlorine ion
K+	Potassium ion
iNOS	Inducible nitric oxide synthase
NMDA	N-methyl-D-Aspartate
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
iGluRs	Ionotropic glutamate receptors
mGluRs	Metabotropic glutamate receptors
nAChRs	Nicotinic acetylcholine receptors
mAChRs	Muscarinic acetylcholine receptors
cGMP	Cyclic guanosine monophosphate
CGRP	Calcitonin gene-related Peptide
NaCl	Sodium chloride
5-HT	5-Hydroxytryptamine
TNF-α	Tissue necrotic factor
AR	Adrenergic receptors

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GPCR	G protein coupled-receptors
Gi	G protein coupled-receptors - inhibitory
Gq	G protein coupled-receptors - activates the phospholipase C
Gs	G protein coupled-receptors - excitatory
NO	Nitric oxide
NOSs	NO synthases
nNOS	Neuronal NOS
iNOS	Inducible NOS
eNOS	Endothelial NOS
ODQ	1-H-[1,2,4]oxadiazolo[4,3-a]quinoxalin-l-one
NK1	Neurokinin-1
NK2	Neurokinin-2
NK3	Neurokinin-3
LD50	Lethal dose 50
EDTA	Ethylenediamine tetra-acetic acid
ALP	Alkaline phosphate
AST	Alanine amino transferase
ALT	Aspartate amino transferase
RBC	Red blood cell count
WBC	White blood cell count
HBG	Hemoglobin concentration
MCH	Mean corpuscular hemoglobin
MCHC	Corpuscular hemoglobin concentration
MCP-1	Monocyte chemoattractant protein
IL-6	Interleukin-6 Gene
IL-10	Interleukin-10 Gene

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L-NOARG	Nω-nitro-L-arginine
L-NAME	NG-nitro-L-arginine-methyl ester
RVM	Rostral ventromedial medulla
MOR1	μ1 receptors
MOR2	μ2 receptors
Kv	Voltage-gated K+ channels
KCa	Ca2+-activated K+ channels
BKCa	Large conductance Ca2+-activated K+ channel

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CHAPTER 1

INTRODUCTION

1.1 Background of study

Pain is the most common reason for patients seeking medical consultation. As the population ages, the number of people seeking medical attention of pain such as low back pain and degenerative disorder is expected to increase (Mills et al., 2019). Thus, the use of medication to relieve pain has always been the primary goal among health care practitioners in pain management. Drugs that use to achieve analgesia, a state of pain relief often called as analgesic drugs or painkiller and can be classified into non-steroidal anti-inflammatory drugs (NSAIDs), opioid and analgesic adjuvants. Although the continuous usage of some commercially available drugs of NSAIDs offers effective analgesia in pain management and inflammation, the prolonged use often associated with serious gastrointestinal ulceration complications or possibly resulting in hospitalization and even death (Goldstein & Cryer, 2015). The consistent use of potent narcotic analgesics such as morphine in treating chronic pain can also associate to kidney failure, liver damage or tolerance (Baldini et al., 2012). The adverse effect profiles from available commercial drugs have prompted researchers to find other alternatives for analgesic drugs with equivalent effects and limited side effects.

Since ancient time, plants have always been used in folk medicine as they are the rich source of bioactive compounds with great efficiency and selectivity. Natural source of these bioactive compounds may contain various therapeutic agents that can potentially become active agents in modern drugs application. In the last decades, the plant-based discovery and development as the source of new drugs have been focusing on the identification and isolation of active metabolites in plants. However, despite the success of the natural product in drug discovery, many huge pharmaceutical companies have decreased their emphasis on natural product research programs. This is due to various reasons including limited supply and access as the authorization approval to collect new samples from the country with natural products is difficult due to the law protecting the flora and fauna. Despite the many challenges, the field of natural products have given rise to many discoveries and developments in organic chemistry (Khan, 2018). Chemical modification of bioactive components of naturally occurring metabolites emerged as one of the widely used method to identify new potential drugs with greater efficacy in the pharmaceutical industry. These discoveries help establish synthetic methodologies and also making it possible to create synthetic analogues of the natural product compounds that is better in terms of its pharmacology and pharmaceutical characteristics (Yadav & Purohit, 2013). Therefore, current research is aimed to explore new agents

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based on the modifications or derivatives of discovered bioactive components from available plants with remarkable therapeutic activities.

Rhizomes such as turmeric have historically used as a household remedy to treat a number of inflammatory-related conditions and disorders in folk medicine such as bowel disease, pancreatitis and rheumatoid arthritis. In addition to its medicinal properties, turmeric or Curcuma longa also gained wide attention among culinary enthusiasts, as it is also used as a seasoning and colouring agent for several food ingredients like mustard, curry, and potato chips (Kumara et al., 2016). Turmeric is composed of several major curcuminoids; curcumin, bisdemethoxycurcumin and demethoxycurcumin. The yellow colour in turmeric is mainly attributed from the presence of these active ingredients (Al-Suhaimi et al., 2011). Among these curcuminoids, curcumin (Figure 1.1) is the dominant polyphenol and responsible for several turmeric's pharmacological activities such as anti-diabetic and anti-inflammatory, as well as exhibits cardio-preventive effect, anti-fertility effect and anti-hypertensive effect (Rahmani et al., 2018). Studies have suggested that two aromatic regions of curcumin might be crucial for potential protein-ligand binding and became a well-accepted design of potential inhibitor (ligand) of protein targets (Lee et al., 2009).

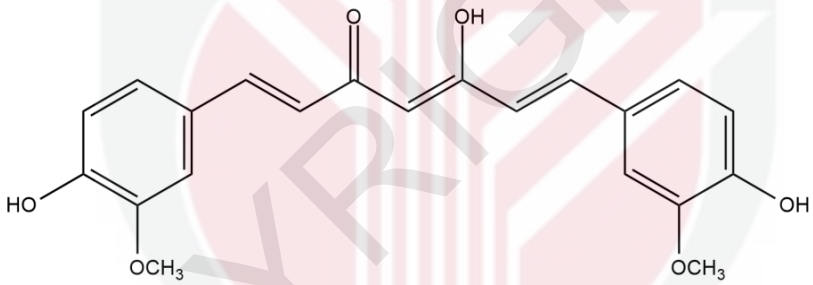

Figure 1.1: Chemical structure of curcumin

1.2 Problem Statement

Although curcumin exhibited excellent anti-inflammatory and antinociceptive activities in vivo and in vitro, the use in medicinal application from curcumin is hindered due to its low bioavailability, solubility and poor absorption rate in the gastrointestinal tract (Sharifi-Rad et al., 2020). Therefore, more research have been done to solve these limitation through various rotes of administration and structural modification of curcumin (Liew et al., 2019). Previously, several diarylpentanoid derivatives from curcuminoids analogues have been successfully synthesized to evaluate their possible anti-inflammatory activity in vitro (Leong et al., 2014). Base from this study, two compound known as 5-(3,4-dihydroxyphenyl)-3-hydroxy-1-(2-hydroxyphenyl)penta-2,4-dien-1-one(DHHPD) and 2-benzoyl-6-(3,4-dihydroxybenzylidene)cyclohexen-1-ol (BDC) significantly

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suppressed the production of nitric oxide (NO) in the interferon gamma (IFN-ɣ)/lipopolysaccharide (LPS)-stimulated RAW 264.7 macrophages. In comparison to the other ninety-six compounds produced, DHHPD (Figure 1.2) and BDC (Figure 1.3) was proposed as the most effective compound as anti-inflammatory agents. Moreover, BDC also demonstrated to have higher solubility in water as compared to curcumin, which is one of the major problems that limits the medicinal properties of curcumin. Furthermore, DHHPD also exerted significant anti-inflammatory and antinociceptive agents in vivo. Based from initial screening, diarylpentanoids showed a promising drug candidates as investigational drug to treat both pain and wounds based on significant antinociceptive and anti-inflammatory properties. The results from other diarylpentanoid reports indicated that BDC could highly be a candidate for further investigation on its potential as a new anti-inflammatory and antinociceptive agents since it comes from the same diarylpentanoids family. Therefore, in vivo evaluation of BDC can further strengthen the medicinal potential of diarylpentanoids compound.

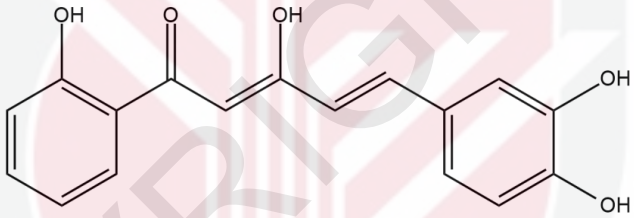

Figure 1.2: Chemical structure of 5-(3,4-dihydroxyphenyl)-3-hydroxy-1-(2-hydroxyphenyl)penta-2,4-dien-1-one

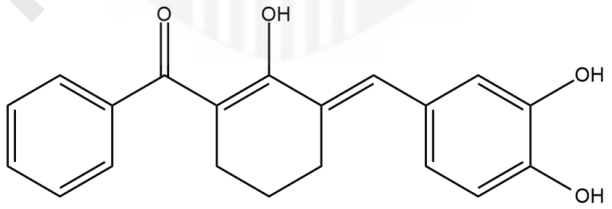

Figure 1.3: Chemical structure of 2-benzoyl-6-(3,4-dihydroxy benzylidene) cyclohexen-1-ol

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1.3 Study Objectives

The general objectives of this study were to investigate the antinociceptive activities of 2-benzoyl-6-(3,4-dihydroxybenzylidene)cyclohexen-1-ol (BDC) and evaluate the mechanisms of action involved in BDC in animal models.

The specific objectives were as follows:

1) To investigate the involvement of opioid receptors in the BDC induced antinociceptive activities.
2) To investigate the involvement of non-opioid receptors systems in the BDC induced antinociceptive activities.
3) To investigate the role of L-Arginine-NO-cGMP-K+ channel pathways in the BDC-induced anti-nociceptive activities.
4) To investigate the role of GABAergic, cholinergic, dopaminergic, noradrenergic, serotonergic and adenosinergic systems.
5) To investigate the involvement of inflammatory mediators in the BDC-induced anti-nociceptive activities.

1.4 Study Hypotheses

The study hypotheses were as follows:

1) BDC exert significant antinociceptive effects through chemical-induced model of preliminary screening.
2) BDC does not related to any characteristic of sedative agents and muscular relaxant properties.
3) The administration of BDC does not exert toxic effect in mice.
4) Opioid receptors are participated in the BDC induced antinociceptive activities.
5) Inflammatory mediators are involved in the BDC-induced antinociceptive activities.
6) L-Arginine-NO-cGMP-K+ channel pathways are involved in the BDC-induced antinociceptive activities.
7) GABAergic, cholinergic, dopaminergic, noradrenergic, serotonergic and adenosinergic systems are involved in BDC-induced antinociceptive activities.

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