EVALUATION OF ANTINOCICEPTIVE ACTIVITY OF 2-BENZOYL-6-(3-BROMO-4-HYDROXYBENZYLIDENE)CYCLOHEXEN-1-OL AND ITS POSSIBLE MECHANISMS OF ACTION IN MICE

By

ONG HUI MING

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

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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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August 2021

Chairman: Dato' Prof. Mohd Roslan Sulaiman, PhD
Faculty: Medicine and Health Sciences

Pain is one of the frequent reasons that one seeks for medical attention. Opiates and of non-steroidal anti-inflammatory drugs (NSAIDs) are the common treatments for various kinds of pain. However, the use of opiates often leads to undesirable effects such as constipation, nausea and even addiction. Besides, prolonged usage of NSAIDs tends to develop gastrointestinal and cardiovascular dysfunctions in one's body. Therefore, there's an urgent need to accelerate the drug discovery for new potent antinociceptive compound with equivalent pain-killing effect as the contemporary analgesics, but with minimal or no adverse effects. The general objective of the present study was to determine the antinociceptive activity of 2-benzoyl-6-(3-bromo-4-hydroxybenzylidene) cyclohexen-1-ol (BBHC) at peripheral and central levels of nociception. Our specific objectives were to study the antinociceptive property of BBHC against peripheral inflammatory mediators, and also to investigate the participation of BBHC in excitatory neurotransmission and central descending inhibitory pathways (opioid and non-opioid pathways). The preliminary antinociceptive activity of BBHC was screened with 3 antinociceptive tests, acetic acid-induced abdominal constriction test, formalin-induced paw licking test and hot plate test. Upon the confirmation of BBHC's inhibitory effect against the chemically- and thermally-induced nociception, BBHC was subjected to investigate for its possible mechanisms of action towards peripherally-mediated inflammatory mediators, excitatory neurotransmitters and a range of pain-modulating receptors from descending inhibitory pathways. The findings from our present study showed that BBHC significantly inhibited chemically- and thermally-induced pain from the 3 antinociceptive screening tests. BBHC had also reduced pain caused by various inflammatory mediators and excitatory neurotransmitters. The antinociception of BBHC was indicated to be associated with descending inhibitory modulations, such as α_2-adrenoreceptor, 5-HT_{1A} receptor, $GABA_A$ receptor, A_1 adenosine receptor, D2-like dopaminergic receptor

and L-arginine-NO-cGMP-K^+ channels pathway. Despite the significant antinociceptive property of BBHC, it was confirmed that BBHC's analgesic activity is not related to muscle relaxation and sedation. BBHC's LD_{50} was proven to be greater than 2000 mg/kg which then classified BBHC as Category 5 according to the globally Harmonised System for classification of chemicals. As conclusion, the present study has shown that BBHC-induced analgesia is mediated by peripheral and central pain modulations of peripheral inflammatory mediators, neurotransmitters and descending inhibitory pathways.

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

PENILAIAN AKTIVITI ANTINOSISEPTIF 2-BENZOYL-6-(3-BROMO-4-HYDROXYBENZYLIDENE)CYCLOHEXEN-1-OL DAN MEKANISME TINDAKANNYA YANG BERPOTENSI DALAM MENCIT

Oleh

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Ogos 2021

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Kesakitan merupakan salah satu sebab utama yang menyebabkan seseorang individu perlu mendapatkan rawatan perubatan. Opiat dan ubat anti-radang bukan steroid (NSAIDs) adalah rawatan umum untuk merawati pelbagai jenis kesakitan. Namun, penggunaan opiat sering membawa kesan negatif seperti sembelit, keloyaan serta ketagihan. Selain itu, penggunaan NSAID yang berpanjangan akan menyebabkan penyakit-penyakit yang berkaitan dengan sistem penghadaman dan kardiovaskular. Oleh itu, terwujudnya keperluan untuk penemuan ubat antinosiseptif baharu yang mempunyai kesan tahan sakit yang setara dengan ubat analgesik yang sedia ada di pasaran, tanpa memberikan kesan buruk atau hanya memberikan kesan buruk yang minima kepada pengguna ubat. Objektif utama bagi kajian penyelidikan ini adalah untuk mengenalpasti aktiviti antinosiseptif bagi 2-benzoyl-6-(3-bromo-4-hydroxybenzylidene)cyclohexen-1-ol (BBHC) secara periferal dan pusat. Objektif khusus kami adalah untuk mengkaji sifat antinosiseptif BBHC terhadap pengantara keradangan periferal, dan juga untuk menyiasat penglibatan BBHC dengan neurotransmiter dan laluan perencatan menurun (melalui sistem opioid dan sistem bukan opioid). Aktiviti antinosiseptif BBHC disaring dengan 3 ujian antinosiseptif asas, iaitu ujian penggeliatan abdomen dengan asid asetik, ujian jilatan tapak dengan formalin dan ujian plat panas. Apabila aktiviti antinosiseptif BBHC terhadap kesakitan yang disebabkan oleh bahan kimia dan haba telah disahkan, BBHC disambungkan dengan ujian mekanisme tindakannya terhadap pengantara keradangan periferal, neurotransmiter dan pelbagai reseptor dari laluan perencatan menurun. Hasil kajian kami menunjukkan bahawa BBHC dapat menghalang kesakitan yang berpunca daripada 3 ujian antinosiseptif asas. BBHC juga mampu mengurangkan kesakitan yang disebabkan oleh pelbagai pengantara keradangan periferal dan neurotransmiter. Aktiviti antinosispetif BBHC telah dikaitkan dengan modulasi perencatan menurun, seperti α_2-adrenoreseptor, reseptor 5-HT_{1A}, reseptor $GABA_A$, reseptor adenosin A_1, reseptor dopaminergik-D2 dan laluan saluran L-arginine-NO-cGMP-K^+.

Aktiviti antinosiseptif BBHC juga dibuktikan bahawa ia tidak berkaitan dengan sebarang kelonggaran otot dan kesan sedasi. LD_{50} BBHC adalah lebih tinggi daripada 2000 mg/kg yang kemudiannya mengelaskan BBHC sebagai pengelasan bahan kimia Kategori ke-5 berdasarkan Sistem Harmonisasi Global. Sebagai kesimpulan, kajian ini telah menunjukkan bahawa kesan analgesia periferal dan pusat yang ditunjukkan oleh BBHC merupakan kesan penglibatan di antara pengantara keradangan periferal, neurotransmiter dan laluan perencatan menurun.

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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 Doctor of Philosophy. The members of the Supervisory Committee were as follows:

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LIST OF ABBREVIATIONS

NSAIDs	Non-steroidal anti-inflammatory drugs
BHMC	2,6-bis-(4-hydroxy-3-methoxybenzylidene)cyclohexanone
CLP	Cecal ligation and puncture
BBHC	2-benzoyl-6-(3-bromo-4-hydroxybenzylidene)cyclohexen-1-ol
BDC	2-benzoyl-6-(3,4-dihydroxybenzylidene)cyclohexen-1-ol
NO	Nitric oxide
IFN-γ	Interferon gamma
LPS	Lipopolysaccharide
IC_{50}	Half maximal inhibitory concentration
μM	Micromolar (10^{-6} mol/L)
cGMP	Cyclic guanosine monophosphate
K^+	Potassium ion
ATP	Adenosine triphosphate
ANOVA	Analysis of Variance
ASA	Acetylsalicylic acid / Aspirin
DMSO	Dimethyl sulfoxide
NaCl	Sodium chloride
ED_{50}	Effective dose for 50% of the inhibiton
LD_{50}	Median lethal dose
CI	Confidence interval
COX	Cyclooxygenase
LOX	Lipooxygenase
TRPA1	Transient receptor potential ankyrin 1
CSZ	Capsazepine

TRPV1	Transient receptor potential vanilloid 1
COX-2	Cyclooxygenase-2
5-HT	5-hydroxytryptamine
PMA	Phorbol-12-myristate-13-acetate
PLC	Phospholipase C
PKC	Protein kinase C
PLA_2	Phospholipase A_2
PIP_2	Phosphatidylinositol-4,5-bisphosphate
NMDA	N-methyl-D-aspartate
AMPA	2-amino-3-(3-hydroxy-5-methyl-isoxazol-4-yl)
mGluRs	Metabotropic glutamate receptors
cAMP	Cyclic adenosine monophosphate
GPCR	G protein-coupled receptors
CGRP	Calcitonin gene-related peptide

CHAPTER 1

INTRODUCTION

Overview

Pain is the main cause for people to visit healthcare institutions for medical consultation and assistance. Pain is an unpleasant yet necessary sensation in the defence system for humans. The pain sensation is essential in providing a prompt warning to the nervous system in order to minimize further tissue damage. However, if the acute pain does not receive proper treatment, the underlying pathological cause(s) of the pain might get worsen and eventually develop into chronic pain. The persistency of chronic pain often affects the quality of life negatively along with some health and well-being issues, such as poor relationships, cognitive disabilities and incompetence to work (Rustoen et al., 2008).

Pain is a common problem that is plaguing the individuals as well as society at a global scale. Based on the result from the Global Burden of Diseases, Injuries, and Risk Factors Study in 2017, pain-related diseases such as lower back pain and neck pain, has been one of the leading causes of non-fatal health loss for almost three decades (Disease, Injury, & Prevalence, 2017). The annual economic burden resulted from back pain alone is estimated to cost over 20% of a country's total health expenditure or 3 times the total cost of all cancer types (Phillips, 2006). Therefore, it is crucial to treat acute pain at the initial phase to prevent the intolerable chronic pain as well as the undesirable emotional, social and financial stress.

Understanding the pain pathway is crucial in the investigation of potential pain-killer drug and its possible mechanisms of action. During inflammation and/or tissue injury, various endogenous inflammatory mediators are released due to vasodilatation and enhanced vascular permeability (Sawynok & Liu, 2003). Upon the stimulation and sensitisation of the primary afferent nociceptors by these mediators, pain impulses are generated and transmitted along the peripheral nerve fibres to central terminals in spinal cord. In the dorsal horn of spinal cord, the primary afferent neurones release excitatory neurotransmitters to excite the second order neurones (Schliessbach & Maurer, 2017). The transmission of pain impulses is continued through second order neurones to the brain stem and thalamus which results in the pain modulation via descending pain modulatory pathway. Till date, many drugs with the ability to attenuate pain transmission and promote anti-pain modulation have been discovered to provide better pain treatment.

Problem Statement and Justification of Present Study

Drugs with prevalent pain-relieving action are commonly referred as analgesics or antinociceptive drugs. The most common treatment for a broad range of pain is the clinical application of non-steroidal anti-inflammatory drugs (NSAIDs) and opiates (Jacklin et al., 2015).

Opioid analgesic compounds such as opium, morphine, and codeine, as well as nonsteroidal anti-inflammatory drugs (NSAIDs) like ibuprofen and aspirin are some of the modern-days analgesics used to treat pain (Watcha & White, 1992). Opioid analgesic compounds work by suppressing the release of excitatory neurotransmitters from nerve terminals and thereby inhibiting the transduction of nociceptive stimuli (Stromgaard K, 2009). NSAIDs on the other hand works by antagonizing the activity of COX 1 and 2 and hence prevent the production of prostaglandin and thromboxane (Hata & Breyer, 2004; Kawabata, 2011).

Although these contemporary available analgesics have highly effective pain control in assorted pathological conditions, various adverse effects often develop along with the administration of these analgesics. The use of opioid analgesic compounds is often associated with constipation, nausea, vomiting and sometimes addiction problems (Rao & Knaus, 2008). While the use of NSAIDs is commonly associated with gastrointestinal issues such as gastrointestinal bleeding, perforation, renal function disturbance as well as cardiovascular problem (Antman et al., 2007; Kawabata, 2011). Hence, these undesirable adverse effects of the current pain-killing drugs have created great awareness and the urgent need to accelerate the drug discovery for new potent antinociceptive compounds with equivalent effects of the contemporary analgesics, yet without or with limited adverse effects.

BBHC As A Novel Diarylpentanoid Analogue

Curcumin has received tremendous attention from the scientific community due to its extensive range of pharmacological properties with minimum adverse side effects (Gupta et al., 2013; Naik et al., 2011; Yang et al., 2008). Unfortunately, the practical application of curcumin is hindered by its poor absorption, low stability and rapid systemic elimination, leading to poor bioavailability and hence a reduced effectiveness in clinical trials (Anand et al., 2007; Mirzaei et al., 2017; Tsuda, 2018). For these reasons, scientists have been working on to modify the chemical structure of curcumin in order to overcome its structural weaknesses.

Diarylpentanoids are considered as the analogues of curcumin, with structural difference whereby the longer heptane bridge is replaced with a shorter pentane bridge as shown in Figure 1 and 2 (Leong et al., 2014). Diarylpentanoids have then gained great attention from the researchers for their outstanding

pharmacological properties and most importantly, they possess better bioavailability as compared to curcumin (Leong et al., 2014).

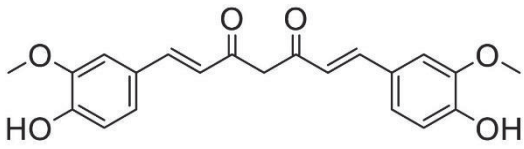

Figure 1: The structure of curcumin.

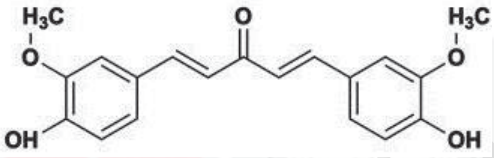

Figure 2: The structure of diarylpentanoid.

In year 2011, our research group had synthesised and demonstrated a diarylpentanoid, named 2,6-bis-(4-hydroxy-3-methoxybenzylidene) cyclohexanone (BHMC), to be an excellent anti-inflammatory compound in inhibiting lethality of cecal ligation and CLP-induced sepsis (Tham et al., 2011). The BHMC compound was also reported to show significant dose-dependent antinociceptive activity in chemical- and thermal-induced murine models (Ming-Tatt et al., 2012).

However, another novel diarylpentanoid analogue of curcumin with the integration of α,β-unsaturated β-diketone and cyclohexanone moieties, called as 2-benzoyl-6-(3-bromo-4-hydroxybenzylidene)cyclohexen-1-ol (BBHC), was chosen as the potential antinociceptive candidate in the present study. This is because BHMC contains 2 phenol groups while BBHC contains only one phenol group (Figure 3). Since phenol group could be toxic, BBHC is speculated to exhibit better safety profile than BHMC. Therefore, if BBHC possesses similar or better antinociceptive activity than BHMC, it will be a better and safer antinociceptive agent than BHMC.

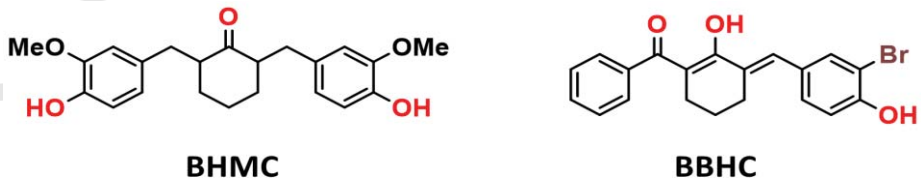

Figure 3: The comparison between the chemical structures of BHMC and BBHC.

In the previous *in vitro* study, BBHC was examined for its nitric oxide (NO) inhibitory property in IFN-γ/LPS-induced RAW 264.7 macrophages (Leong et al., 2015). NO plays an important role in pain pathway because it is a mediator that involves in both peripheral and central levels of nociception. Interestingly, BBHC had shown strong NO inhibition, with IC_{50} value of 15.2 μM as compared to other analogues in the new series of diarylpentanoids (Leong et al., 2015). Moreover, another member from the same novel series of analogues, 2-benzoyl-6-(3,4-dihydroxybenzylidene)cyclohexen-1-ol (BDC), also exhibited antinociceptive activities at both the peripheral and central levels using chemical- and thermal-induced pain models (Ahmad Farhan Ahmad Azmi et al., 2016).

Gathering our positive outcomes with derivatives from our novel series analogues (BHMC and BDC), along with the encouraging *in vitro* cell-based results obtained using BBHC, we hypothesised that BBHC will have equivalent or more potent antinociceptive properties as BHMC or BDC at peripheral and central levels, which also warrant a more in-depth future study using animal pain models.

Objectives of The Study

The general objective of the present study was to determine the peripheral and/or central antinociceptive activity of BBHC by using chemical- and thermal-induced nociceptive mice models.

The specific objectives were to:

1. Investigate the involvement of peripherally-mediated inflammatory mediators in the BBHC-induced antinociceptive activity
2. Investigate the involvement of excitatory neurotransmitters in the BBHC-induced antinociceptive activity
3. Determine the involvement of central opioid receptor and its subtypes in the BBHC-induced antinociceptive activity
4. Explore the involvement of central non-opioid descending inhibitory pathways in the BBHC-induced antinociceptive activity
5. Examine the involvement of L-arginine-NO-cGMP-ATP-sensitive K^+ channel pathway in the BBHC-induced antinociceptive activity
6. Study the involvement of potassium channels in the BBHC-induced antinociceptive activity
7. Analyse the acute toxicity profile of BBHC

Research Framework of The Study

The research framework of the present study is demonstrated as follows:

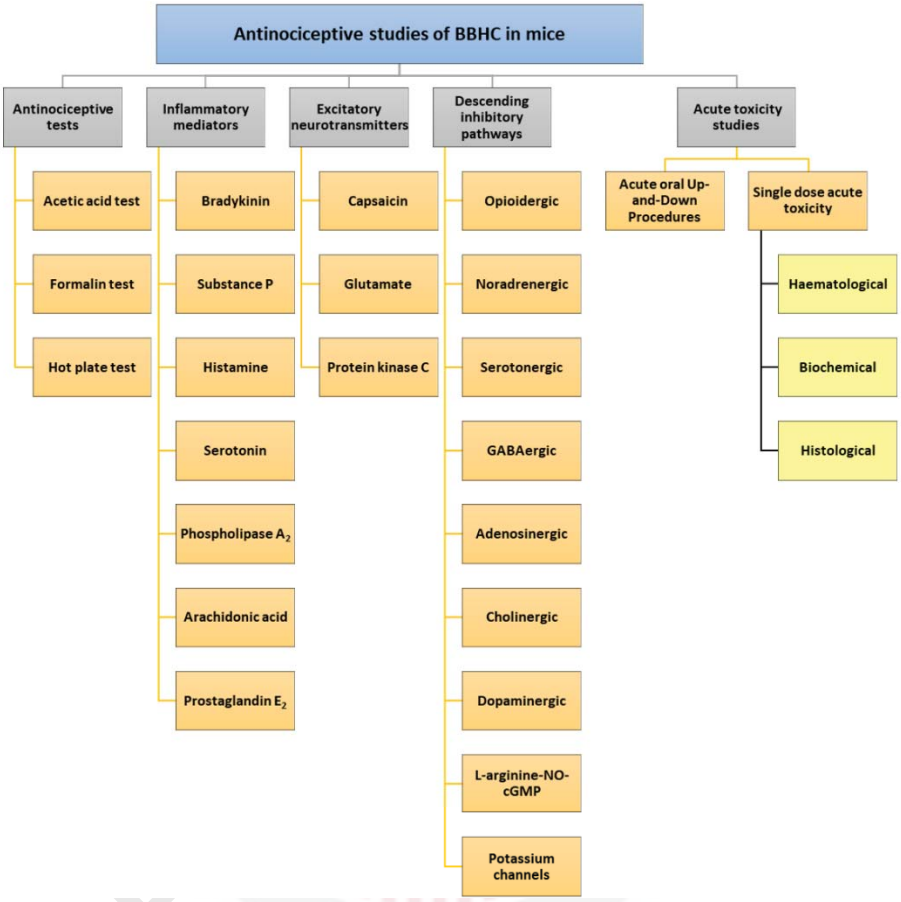

Figure 4: The research framework of the present study.

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