UNIVERSITI PUTRA MALAYSIA

ANTINOCICEPTIVE AND ANTI INFLAMMATORY ACTIVITIES OF 3-(2,5 DIMETHOXYPHENYL)-1-(5 METHYLFURAN-2-YL) PROP-2-EN-1 IN MICE.

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By

NOOR AZLINA BINTI ABU BAKAR

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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August 2016

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

Chalcone is being extensively explored due to its pharmacological properties. The search on chalcone derivatives as an analgesic agent increased as the current pain treatment caused severe side effects. This study aimed to determine the analgesic activity of new chalcone derivative, 3-(2,5-dimethoxy phenyl)-1-(5-methyl furan-2-yl) prop-2-en-1 (DMPF-1) and to identify its possible mechanism of actions. Analysis of acute and sub-acute toxicity of DMPF-1 supplementation was performed. A single oral dose (1000 mg/kg) and 28-days repeated treatment of DMPF-1 (0.1-10 mg/kg) showed no significant changes in body weight, haematological, serum biochemical, macroscopic and microscopic analysis proved the absence of changes in the treated subjects. Antinociceptive study of DMPF-1 was started using the acetic acid-induced abdominal writhing test, formalin-induced paw licking test and hot plate test. The results showed DMPF-1 significantly reduce pain in a dose-dependent manner and suggests central and peripheral antinociceptive effect. Accordingly, the study on the possible involvement of opioid receptors was done. The challenge of DMPF-1 with naloxone showed no reversion of its antinociceptive effect, suggesting no contribution to the opioid system. Further examination using capsaicin, glutamate and phorbol 12-myristate 13-acetate (PMA)-induced paw licking test showed that the systemic administration of DMPF-1 at various doses significantly reduced the nociceptive response of the mice in a dose-dependent manner. This result proposed that DMPF-1 was acted through the vanilloid, glutamatergic and protein kinase C system in mediating analgesic action. In addition, the pre-treatment of DMPF-1 with L-arginine and ODQ had reversed the DMPF-1 antinociceptive effect indicating the involvement of nitric oxide and cyclic GMP

synthesis. In sequence, pre-treatment of the animals with various potassium channels blockers such as charybdotoxin, glibenclamide and tetraethylammonium significantly abolished its antinociceptive activity, which suggests the facilitation of NO-cGMP pathway, large Ca2+ activated, ATP sensitive, and voltage-dependent potassium channels in its mechanism of action implied. At present, the possible involvement of various inhibitory neuroreceptors was performed. Pre-treatment with bicuculine appears to block its antinociceptive profile in which the event was not seen in pre-treatment with phaclofen, thus suggesting the involvement of the GABAA receptor. Meanwhile, pre-treatment of the subject with haloperidol and metoclopramide was carried out to investigate the involvement of dopaminergic receptors. Marked inhibition of DMFP-1 activity by only metoclopramide was observed, which indicated the contribution of the D2 dopaminergic receptor. Further investigation using atropine, yohimbine, and caffeine attenuated its antinociceptive action, thus suggesting those receptors' participation in pain modulation. Moreover, pre-treatment of the mice with various serotonergic receptor antagonists, including WAY 100635, pindolol and kentanserin but not ondansetron, however, fail to affect the antinociceptive activity of DMPF-1. This concludes that DMPF-1 could stimulate the 5HT3 receptor in order to produce antinociception. A paw oedema test was carried out to determine its peripheral antinociceptive capability. DMPF-1 at various dosages can reduce the volume of paw oedema induced by carrageenan, bradykinin, substance P, prostaglandin E, histamine, arachidonic acid and serotonin. Results indicate that DMPF-1 exerts peripheral activity by attenuating the action of the inflammatory mediators. In conclusion, this study confirms the antinociceptive activities of DMPF-1 and elucidates the possible mechanism of action through which it exerts its antinociceptive effects.

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

AKTIVITI ANTINOSISEPTIF DAN ANTIRADANG DARI SEBATIAN CHALCONE 3-(2,5 DIMETHOXYPHENYL)-1-(5 METHYLFURAN-2-YL) PROP-2-EN-1 DALAM MENCIT

Oleh

NOOR AZLINA BINTI ABU BAKAR

Ogos 2016

Pengerusi : Profesor Mohd Roslan Sulaiman, PhD
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Chalcone dikaji secara meluas disebabkan oleh sifat farmakologinya yang memberangsangkan seperti antiradang dan antiproliferatif. Kesan sampingan oleh agen analgesia yang digunakan pada hari ini menyebabkan kajian terhadap c*halcone* dan sebatiannya semakin meningkat. Kajian ini bertujuan untuk menentukan aktiviti antinosiseptif oleh sebatian *chalcone* baharu, 3-(2,5-dimethoxyphenyl)-1-(5-methylfuran-2-yl) prop-2-en-1 (DMPF-1) dan mengenalpasti mekanisme tindakannya. Analisis ketoksikan akut dan sub akut terhadap rawatan dengan DMPF-1 telah dilakukan. Pemberian DMPF-1 sebagai dos oral tunggal (1000 mg/kg) dan rawatan berulang selama 28 hari (0.1 - 10 mg/kg) tidak menunjukkan sebarang kesan toksik terhadap subjek termasuk kesan motiliti. Tiada perubahan signifikan pada berat badan, parameter hematologi, biokimia serum, makroskopik dan mikroscopik diperhatikan. Penetuan antinosiseptif oleh sebatian *chalcone* dimulakan dengan ujian pengeliatan aruhan asid asetik, ujian penjilatan tapak kaki aruhan formalin dan ujian ceper panas. Keputusan menunjukkan bahawa DMPF-1 berkebolehan mengurangkan kesakitan secara signifikan mengikut perkadaran dos. Ini menunjukkan penglibatan sistem periferi dan pusat dalam aktiviti antinosiseptif sebatian ini. Seterusnya, kajian terhadap penglibatan sistem reseptor opioid dijalankan dengan antagonis tidak selektif bagi reseptor opioid, naloxone. Tiada sebarang perubahan terhadap kesan antinosiseptif DMPF-1 ditunjukkan membuktikan bahawa penglibatan sistem opioid tidak berlaku. Kajian selanjutnya dijalankan menggunakan model penjilatan tapak kaki aruhan kapsaisin, glutamat dan phorbol 12-myristate 13-acetate (PMA). Keputusan menunjukkan pemberian DMPF-1 (0.1-5.0 mg/kg) secara sistemik mengurangkan kesan nosiseptif secara signifikan. Keputusan ini menunjukkan bahawa DMPF-1 bertindak menerusi sistem vanilloid, glutamatergik dan protein kinase C dalam aktiviti analgesianya. Penilaian diteruskan untuk

menentukan penglibatan nitrik oksida dan siklik GMP diikuti dengan pengaktifan saluran kalium. Prarawatan DMPF-1 dengan L-arginina atau ODQ telah merencatkan kesan antinosiseptif DMPF-1 justeru membuktikan penglibatan saluran ini. Seterusnya, prarawatan dengan pelbagai jenis antagonis saluran kalium; charybdotoxin, glibenclamide dan tetraethylammonium secara signifikan merencatkan kesan antinosiseptif sebatian *chalcone* ini. Penglibatan laluan NO-cGMP, saluran kalium konduktan besar yang diaktifkan oleh kalsium, saluran kalium sensitif terhadap ATP dan saluran kalium kebergantungan voltan dalam mekanismenya ditunjukkan. Selain itu, terdapat pelbagai neuroreseptor perencatan sebagai target terapi seperti GABAergik, adrenergik, serotonergik, adenosinergik dan kolinergik. Dengan ini, kemungkinan penglibatan oleh reseptor tersebut dalam aktiviti antinosiseptif DMPF-1 dikaji. Prarawatan dengan bicuculine, telah merencatkan kesan antinosiseptif *chalcone* justeru menunjukkan penglibatan reseptor $GABA_A$. Sementara itu, prarawatan dengan haloperidol dan metoclopramide; iaitu antagonis terhadap receptor D2 dopaminergik telah dilakukan untuk menyiasat penglibatan reseptor tersebut. Menerusi kajian, aktiviti DMPF-1 telah disekat hanya oleh metoclopramide dan menunjukkan penglibatan reseptor D2 dopaminergik. Tambahan pula, kajian menggunakan atropine; antagonis reseptor muskarin korlinergik, yohimbine; antagonis reseptor α_2 dan kafiena iaitu antagonis tidak selektif adenosinergik telah menghalang aktiviti antinosiseptif DMPF-1 membuktikan penyertaan reseptor terbabit dalam modulasi nosiseptif. Juga, prarawatan dengan ondansetron iaitu antagonist kepada reseptor $5HT^3$ telah merencatkan aktiviti antinosiseptif sebatian ini. Ini menunjukkan bahawa reseptor $5HT^3$ turut terlibat dalam menghasilkan antinosiseptif sebatian DMPF-1. Untuk meneruskan kajian terhadap kesan antinosiseptif periferi oleh DMPF-1, ujian edema tapak kaki dijalankan. Pemberian DMPF-1 secara sistemik pada dos pelbagai antara 0.1 mg/kg hingga 10 mg/kg berupaya mengurangkan edema tapak kaki aruhan karagenan. Kajian diteruskan dengan edema tapak kaki aruhan pelbagai mediator kimia termasuk bradikinin, sebatian P, prostaglandin E, histamin, asid arakidonik dan serotonin. DMPF-1 berupaya mengurangkan edema tapak kaki yang diaruhkan oleh setiap satunya, menunjukkan bahawa sebatian ini bertindak pada periferi dengan merencatkan aktiviti mediator tersebut. Sebagai kesimpulan, kajian ini menunjukkan aktiviti antinosiseptif DMPF-1 yang signifikan, serta mekanisme tindakan yang terlibat.

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I certify that a Thesis Examination Committee has met on 22 August 2016 to conduct the final examination of Noor Azlina binti Abu Bakar on her thesis entitled "Antinociceptive and Anti-inflammatory Activities of Chalcone Derivative 3-(2,5 dimethoxyphenyl)-1-(5 methylfuran-2-yl) prop-2-en-1-one (DMPF-1) in Mice Model" 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 Doctor of Philosophy.

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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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5-HT	5-hydroxytryptamine
AA	Arachidonic Acid
Ach	Acetylcholine
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AMPA	a-amino-3-hydroxy-5-ethylisoxazole-4-propionic acid
ANOVA	Analysis of variance
ASA	Acetylsalicylic Acid
AST	Amino Transferase
B1	Bradykinin 1
B2	Bradykinin 2
BBB	Blood Brain Barrier
BDNF	Brain-derived neurotrophic factor
BK	Bradykinin
Ca^{2+}	Calcium Ion
CGRP	Calcitonin gene related peptide
CNS	Central Nervous System
COX-1	Cyclooxygenase 1
COX-2	Cyclooxygenase 2
DA	Dopamine
DMPF-1	3-(2,5 dimethoxyphenyl)-1-(5-methylfuran-2-yl) prop-2-en-1-one
DRG	Dorsal root ganglion
EDTA	Ethylenediaminetetraacetic Acid Anticoagulant

EP	prostanoid E receptor
g	Gram
GABA	Gama amino butyric acid
GDNF	Glial cell line-derived neurotrophic factor
Gi	G inhibitory
Gs	G stimulatory
H&E	Haematoxylin and Eosin
Hb	Haemoglobin
i.p.	Intraperitoneal
i.pl.	Intraplantar
IASP	International Association for the Study of Pain
ICR	Imprinting Control Region
KA	Kainic acid
Kg	Kilogram
LOX	Lipoxygenase
M	Molar
mg	Milligram
mL	Millilitre
NA	Noradrenaline
Na+	Sodium Ion
NaCl 0.9%	Normal Saline
NGF	Nerve growth factor
NMDA	N-methyl-D-aspartate
NO	Nitric Oxide
NSAIDs	Non-steroidal anti-inflammatory drugs
OECD	Organization for Economic Co-operation and Development

PBS	Phosphate-buffered saline
p.o.	Per Oral
PGE2	Prostaglandin E2
PLA2	Phospholipase A2
PLC	Phospholipase C
PNS	Peripheral Nervous System
RBC	Red Blood Cell
S.E.M	Standard Error of Mean
SAIDs	Steroidal anti-inflammatory drugs
SP	Substance P
TRPV1	Transient Receptor Potential Vanilloid 1
WBC	White Blood Cell

CHAPTER 1

INTRODUCTION

Pain was clearly defined by International Association for the Study of Pain (IASP) as an unpleasant sensory and emotional experience associated with either actual or potential tissue damage. Physiologically, pain is not a merely physical experience but is a complex mechanism of sensory modalities that is important for detection, protection and response against real and potential tissue injuries. However, poor pain management always led to serious problems thus affecting individual's quality of life.

For centuries, various natural sources was being used as medications to reduced pain sensation. For example poppy (*Papaver somniferum*) and willow bark (*Salix spp*). In the 19th century, scientists found that there are active ingredient from natural sources such as morphine and salicin that are responsible in mediating pharmacological effects. The medicinal properties of these natural compound were appreciated and open a great interest in Greek physicians thus leading to the development of an analgesic agent known as acetylsalicylic acid (ASA).

Steroidal anti-inflammatory drugs (SAIDs), non-steroidal anti-inflammatory drugs (NSAIDs) and opiates are currently practiced as a mainstay of pain relief agents and available for more than centuries. However, continuous consumption of those medications lead to undesirable side effects in a worst case scenario might be lethal due to damages of the internal organ such as liver, kidney and stomach. Alternately, proton pump inhibitor (PPI) and cyclooxygenase-2 (COX-2) inhibitor was also used in conjunction with the traditional medicine as to reduce the risk of said side effects but was also prove to be ineffective. The adverse side effects of the prescribed medications call our attention to the importance in screening and finding an alternative that will hopefully has analgesic property with lesser or no side effect than current drugs.

The search of new medicine from various plant-based compounds has seen fruitful and logical research strategies. One of promising compounds found in the plant is chalcone. Chalcone belongs to flavonoid family (Nowakowska, 2007). Chemically, they consist of an open-chain flavonoids bearing two aromatic rings linked by a three-carbon α,β-unsaturated carbonyl system (Orlikova et al., 2011). As a flavonoid, chalcone was found to be one of the important compounds that is responsible for pharmacological activities. The ethno pharmacological effect of chalcone-containing plant such as Piper, *Piper methysticum* and *Glycyrrhiza* were long been revealed previously throughout certain region especially in Asia, Africa and Brazil.

Recent study in our lab reported that chalcone isolated from kava-kava plant possessed an antinociceptive activity in three different assays and may have potential in developing analgesic drugs (Mohamad et al., 2010). In the study, flavokawain B reported to have both peripheral and central antinociceptive effects. Furthermore, the inhibitory effect possessed by this isolated chalcone was 68 fold more effective than commercially analgesic acetylsalicylic acid (ASA) in acetic acid-induced abdominal writhing assay. Various possible mechanisms of flavokawain B were also revealed in the study (Mohamad et al., 2011).

Apparently, chalcone isolated from natural sources and its derivatives are versatile and promising as analgesic candidates. Several studies had found that the synthetic derivatives of chalcone are capable to inhibit the synthesis of prostaglandins (PG) and nitric oxide (NO) which are products of the nitric oxide synthase (NOS) and cyclooxygenase (COX) pathways, respectively (de Campos-Buzzi et al., 2007). In vitro study using IFN-c/LPS-activated RAW 264.7 macrophages cells showed that chalcones bearing furanyl group bared remarkable anti-inflammatory activity since they inhibit the production of NO and PGE2 which is responsible for inflammatory process (Rojas et al., 2002).

Modification of chalcone is important in order to suppress or improve certain characteristic of the compound including their bioavailability, polarity, stability, binding efficacy and efficiency towards targeted receptors. Based on the recent reports, 3-(2,5-dimethoxyphenyl)-1-(5-methylfuran-2-yl) prop-2-en-1-one or known as DMPF-1; new derivative of chalcone was synthesized. They assign similar backbones to the natural chalcone and it is proposed that this novel compound might have the similar or more persuasive analgesic profile.

The significance of this study is to provide an evidence of the pharmacological activity of DMPF-1 compound especially in antinociceptive and anti-inflammatory activities using mice models. This scientific research also conducted to assess the potential central and peripheral effect of this compound together in finding its possible mechanism of actions. As the aims of this study is to find an alternative persuasive analgesic agent with fewer or no side effects towards the subject, the toxicological finding also included in this study. Apart from strengthening the versatility of chalcone pharmacological effect, this study may as well useful for further references.

1.1 Problem of Statement

Treatment of pain using general analgesic agents such as non-steroidal anti-inflammatory drugs (NSAIDs), Steroidal anti-inflammatory drugs (SAIDs), opioid analgesic, muscle relaxant, adjuvant analgesic and many more are effective in combating pain. However consumption these drugs usually have adverse side effects or that to certain extend might interfere with normal

physiological process of the body such as in the case of cyclooxygenase (COX) inhibitors (James 1999).

NSAIDs mediates its action by inhibiting COX enzyme activities, thus limiting or inhibits the production of prostaglandin. In addition, non-selective COX inhibitors will inhibits both COX-1 and COX-2 enzymes and this will create adverse effects in gastrointestinal tract, kidneys as well as platelet system (Gadzhanova et al., 2013). Even though COX-2 inhibitor could minimise the side effects on the gastrointestinal tract but it may increase the risk of myocardial infarction, stroke and even death. Opioid analgesic usually involves in the inhibition of nociception from periphery to the spinal cord due to its affinity to bind with the opioid receptors in central nervous system. Most common side effects of opioid drugs may include sedation, dyspnoea, urine retention, nausea and vomiting (Thompson et al., 2005).

Due to problem stated, studies and researches must be carried out to find a new compound or a new alternative in treating pain with little or no side effects. Compound based on the natural product draw great attention and popular in modern medicine due to its widespread usage in traditional medicine.

1.2 Hypothesis

Treatment with DMPF-1 compound are capable to produce an antinociceptive and anti-inflammatory activity.

1.3 Objective

The objectives of this research are to determine the potential antinociceptive and anti-inflammatory activity of new chalcone derivative (DMPF-1) and its possible mechanisms of action.

1.4 Specific Objective

a) To determine the possible acute toxicity effect of DMPF-1 treatment on motility, behavioural changes, serum biochemical profile, macroscopic and microscopic evaluation of the kidney, liver and stomach.
b) To evaluate the central and peripheral antinociceptive properties of DMPF-1 compound and its possible mechanisms of action involved using animal model.
c) To assess the interaction of DMPF-1 treatment towards TRPV-1 receptor, glutamate, L-arginine/nitric oxide, potassium channel,

GABAergic, noradrenergic, adenosinergic, serotonergic and cholinergic receptors.

d) To evaluate the possible anti-inflammatory effect of the compound and its possible mechanisms of action involved.

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