UNIVERSITI PUTRA MALAYSIA

EFFECTS OF CARDAMONIN ALLEVIATE HYPERALGESIA AND ALLODYNIA WITH POSSIBLE INVOLVEMENT OF MONOAMINERGIC PATHWAYS IN CHRONIC CONSTRICTION INJURY-INDUCED NEUROPATHIC PAIN MICE MODEL

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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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Chair : Associate Professor Dr. Enoch Kumar A/L Perimal, PhD
Faculty : Medicine and Health Sciences

Neuropathic pain is chronic pain caused by the nerve's injury that accompanied with changes in the somatosensory system which is normally presented with hyperalgesia and allodynia. The mechanism of this condition is complex, hence, neuropathic pain patient frequently does not receive a significant benefit from current treatments. This situation might be due to an ineffective dose given, numerous adverse effects and drug delivered is not specific to the target. Nevertheless, our previous study on neuropathic pain discovered that cardamonin (a naturally occurring chalcone) have the potential to alleviate neuropathic pain symptoms in the chronic constriction injury (CCI) mice model. Hence, this present study aimed to further evaluate the possible monoaminergic pathway's involvement in cardamonin induced antihyperalgesic and antiallodynic effects in CCI mice model. The chronic constriction injury model was performed by placing one loose ligation on the ICR male mice's sciatic nerve to develop neuropathic pain condition. Day 14 post-surgery, four different cardamonin doses of 0.3, 3. 1 and 10 mg/kg were administered intraperitoneally to determine the effective dose of cardamonin to alleviate hyperalgesia and allodynia. The behavioral responses were assessed using the Hargreaves plantar test (thermal hyperalgesia) and the von-Frey filament test (mechanical allodynia). Cardamonin at 10mg/kg was shown to exhibit a significant anti-hyperalgesia and anti-allodynia properties in the CCI mouse model. The investigation of serotonergic involvement was performed by depleting the serotonergic level using ρ-chlorophenylalanine (PCPA, 100 mg/kg, i.p), a serotonin synthesis inhibitor, for four consecutive days before cardamonin treatment. Our results indicate the antihyperalgesic and antiallodynic effects of cardamonin were reversed after administration of PCPA. Following this, the mice's pretreatment with several 5-HT receptor subtypes antagonists before cardamonin 10 mg/kg treatment implies that serotonin receptors 1, 1A, 1B, 2A, 3, 6 and 7 were involved in the antihyperalgesic and antiallodynic effect of cardamonin. Further evaluation of protein expression using western blot following cardamonin treatment appear to upregulate the 5-HT_{1A} protein expressions in mice's spinal cord,

brainstem and cerebral cortex. Our finding suggests that cardamonin modulates the 5-HT_{1A} receptor to induce the descending serotonergic inhibitory system, probably via the PAG-RVM-spinal cord pathway activation. Following this, the noradrenergic system's involvement was evaluated by administering non-specific α- and β-adrenergic receptor antagonists before cardamonin treatment. Further investigation into the effect of cardamonin on specific adrenergic receptors subtypes revealed that $\alpha_{1,}$ α_2, β_1 and β_2 was important in cardamonin induced antineuropathic effect in the CCI mice model. Our findings demonstrate that cardamonin can up-regulate α_{2A} receptor expression. This finding suggests the inhibitory effect of cardamonin is likely to be modulated via the upregulation of this receptor activity in the brainstem and spinal cord. Therefore, we postulated that the pain inhibitory effect of cardamonin in CCI-induce mice is probably mediated by the action of serotonin and noradrenergic receptors within the central and peripheral nervous system. Precisely, the inhibitory action of cardamomin might be modulated via 5-HT_{1A} and α_{2A} receptors in the brainstem and spinal cord. In conclusion, our findings demonstrated that monoaminergic pathways were involved in mediating the antineuropathic effect of cardamonin in CCI induced neuropathic pain model and can be a new therapeutic approach for neuropathic pain management.

Abstrak tesis yang dikemukan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk Ijazah Master Sains

KESAN KARDAMONIN DALAM MENGURANGKAN HIPERALGESIK AND ALLODINIA DENGAN KEMUNGKINAN PENGLIBATAN LALUAN MONOAMINERGIK DALAM MODEL CCI-MENGARUH KESAKITAN NEUROPATIK MENCIT

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Kesakitan neuropatik adalah sakit kronik yang disebabkan oleh kecederaan saraf yang disertai dengan perubahan dalam sistem somatosensori yang biasanya ditunjukkan dengan hiperalgesia dan allodynia. Mekanisme keadaan ini adalah kompleks, oleh itu, pesakit kesakitan neuropatik selalunya tidak mendapat manfaat yang ketara daripada rawatan semasa. Keadaan ini mungkin disebabkan oleh dos yang tidak berkesan yang diberikan, banyak kesan buruk daripada ubat diberikan dan ubat yang digunakan tidak khusus kepada sasaran. Walau bagaimanapun, kajian kami yang terdahulu mengenai kesakitan neuropatik mendapati bahawa cardamonin (kalkon semulajadi) mempunyai potensi untuk mengurangkan gejala sakit neuropatik dalam model tikus kecederaan penyempitan kronik (CCI). Oleh itu, kajian ini bertujuan untuk menilai lebih lanjut kemungkinan penglibatan laluan monoaminergik dalam kesan antihiperalgesik dan antiallodynik yang disebabkan oleh cardamonin dalam model tikus CCI. Model kecederaan penyempitan kronik telah dilakukan dengan meletakkan satu ikatan longgar pada saraf skiatika tikus jantan ICR untuk menghasilkan kesakitan neuropatik. Hari ke-14 selepas pembedahan, empat dos cardamonin berbeza seperti 0.3, 3. 1 dan 10 mg/kg telah diberikan secara intraperitoneal untuk menentukan dos cardamonin yang berkesan untuk mengurangkan hiperalgesia dan allodynia. Tindak balas tingkah laku dinilai menggunakan ujian plantar Hargreaves (hiperalgesia terma) dan ujian filamen von-Frey (alodinia mekanikal). Cardamonin pada dos 10mg/kg telah mempamerkan ciri-ciri anti-hiperalgesia dan anti-alodinia yang ketara dalam model tikus CCI. Penyiasatan penglibatan serotonergik dilakukan dengan mengurangkan tahap seratonin menggunakan ρ-chlorophenylalanine (PCPA, 100 mg/kg, i.p), perencat sintesis serotonin, selama empat hari berturut-turut sebelum rawatan cardamonin. Keputusan kami menunjukkan kesan antihiperalgesik dan antialodinik cardamonin telah diterbalikkan selepas pemberian PCPA. Kajian lanjut menggunakan pra-rawatan tikus dengan beberapa antagonis subtipe reseptor 5-HT sebelum rawatan cardamonin 10 mg/kg telah menunjukkan bahawa reseptor serotonin 1, 1A, 1B, 2A, 3, 6 dan 7 terlibat dalam kesan antihiperalgesik dan antialodinik oleh cardamonin. Penilaian lanjut ekspresi

protein menggunakan Western blot selepas rawatan cardamonin berupaya untuk meningkatkan ekspresi protein 5-HT_{1A} dalam saraf tunjang, batang otak dan korteks serebrum tikus. Penemuan kami telah menunjukkan bahawa cardamonin memodulasi reseptor 5-HT_{1A} untuk mendorong sistem perencatan serotonergik menurun, mungkin melalui pengaktifan laluan saraf tunjang PAG-RVM. Berikutan ini, penglibatan sistem noradrenergik juga telah dinilai dengan memberi antagonis reseptor α- dan β-adrenergik yang tidak spesifik sebelum rawatan cardamonin. Penyiasatan lanjut mengenai kesan cardamonin pada subtipe reseptor adrenergik tertentu mendedahkan bahawa α_1, α_2, β_1 dan β_2 adalah penting dalam kesan antineuropatik yang disebabkan oleh cardamonin dalam model tikus CCI. Penemuan kami menunjukkan bahawa cardamonin boleh mengawal selia ekspresi reseptor α_{2A}. Penemuan ini menunjukkan bahawa kesan perencatan cardamonin mungkin dimodulasi melalui pengawalseliaan aktiviti reseptor ini dalam batang otak dan saraf tunjang. Oleh itu, kami mengandaikan bahawa kesan perencatan sakit cardamonin dalam tikus induksi CCI mungkin dimediasi oleh tindakan reseptor serotonin dan reseptor noradrenergik dalam sistem saraf pusat dan periferal. Secara tepatnya, tindakan perencatan cardamomin mungkin dimodulasi melalui reseptor 5-HT_{1A} dan α_{2A} dalam batang otak dan saraf tunjang. Kesimpulannya, penemuan kami menunjukkan bahawa laluan monoaminergik terlibat dalam pengantaraan kesan antineuropatik oleh cardamonin dalam model sakit neuropatik yang disebabkan oleh CCI dan boleh menjadi pendekatan terapeutik baharu untuk pengurusan kesakitan neuropatik.

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Declaration by Members of Supervisory Committee

This is to confirm that:

- the research conducted and the writing of this thesis was under our supervision;
- supervision responsibilities as stated in the Universiti Putra Malaysia (Graduate Studies) Rules 2003 (Revision 2012-2013) are adhered to.

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5-HT	Serotonin
5-HTP	5 Hydroxytryptamine
AADC	Amino Acid Decarboxylase Acid
AC	Adenylyl cyclase
ACC	Anterior Cingulate Cortex
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid
ANOVA	Analysis of Variance
AR	Adrenergic Receptor
BTX-A	Botulinum toxin A
Ca^{2+}	Calcium Ion
cAMP	Cyclic 3'5' Adenosine Monophosphate
CAT	Catalase
CCI	Chronic Constriction Injury
CCK2	Cholecystokinin 2
CGRP	Calcitonin Gene Related Peptide
Cl^-	Chloride Ion
CMHs	Heat and Mechanically Sensitive
CNS	Central Nervous System
COX	Cyclooxygenase
DA	Dopaminergic
DAG	Diacylglycerol
DLF	Dorsolateral Funiculus
DMSO	Dimethyl Sulfoxide
DRG	Dorsal Root Ganglion

EAA	Excitatory Amino Acid
ENK	Enkaphalin
FDA	Food Drug Association
GABA	Γ-aminobutyric acid
GSH	Glutathione
HA	Histaminergic
HIV	Human Immunodeficiency Virus
i.p.	Intraperitoneal
IASP	International Association for the Study of Pain
IL	Interleukin
IP_3	inositol phosphate
K^+	Potassium Ion
LC	Locus Coeruleus
L-Dopa	L-dihydroxyphenylacetic acid
NA	Noradrenaline
NA^{2+}	Sodium Ion
NaCl	Sodium Chloride (Normal Saline)
NeuPSIG	Neuropathic pain Special Interest Group
NF-κB	Nuclear Factor- κB
NGF	Nerve Growth Factor
NMDA	N-methyl-D-aspartate
NO	Nitric Oxide
NOS	Nitric Oxide Synthase
NRM	Nucleus Raphe Magnus
NRTIs	Nucleoside Reverse Transcriptase Inhibitor

PAG	Periaqueductal Grey
PCPA	ρ-chlorophenylalanine
PDN	Peripheral Diabetic Neuropathy
PHN	Postherpetic Neuralgia
PIP_2	Phosphatidylinositol 4,5 Bisphosphate
PLC	Phospholipase C
PNI	Peripheral Nerve Injury
PNS	Peripheral Nervous System
PVDF	Polyvinylidene Fluoride
RVM	Rostral Medial Medulla
SC	Spinal Cord
SCI	Spinal Cord Injury
SI	Primary Somatosensory Cortices
SII	Secondary Somatosensory Cortices
SNRI	Serotonin-Noradrenaline Reuptake Inhibitor
SOD	Superoxide Dismutase
SP	Substance P
TBS	Tris-buffer Saline
TBST	Tris-buffered Saline with Tween 20
TCA	Tricyclic Antidepressant
TNF-α	Tumour Necrosis Factor α
TRP	Transient Receptor Potential
VDCC	Voltage Dependent Calcium Channel
viPAG	Ventrolateral PAG
WDR	Wide Dynamic Range

CHAPTER 1

INTRODUCTION

Pain is a multifaceted sensory experience that intrinsically unpleasant, affecting millions of people worldwide. Acute pain or nociceptive pain is a biological warning to our body from any potential harmful stimuli. In contrast, chronic pain is a pathological condition caused by persistent damage associated with injury or diseases (Carr & Goudas, 1999). Chronic pain arises as a consequence of either inflammatory response accompanied by a substantial nerve impairment or tissue damage (Woolf, 1989) Nociceptive pain is pain due to actual or impending tissue damage of the neural pathway. In contrast, neuropathic pain is a health disorder instigated by the nervous system lesion or dysfunction. In addition, this condition is frequently sustained by several different mechanisms (Nicholson, 2006). Diseases such as postherpetic neuralgia, human immunodeficiency virus (HIV) infection, trigeminal neuralgia and multiple sclerosis are at high risk of developing neuropathic pain (Colloca et al., 2017).

The neuropathic patient commonly experiences a distinct set of symptoms that occur spontaneously, occasionally or only when evoked, such as burning, electrical-like sensation, shooting or stabbing pain (Jensen et al., 2007). This condition is significantly affecting patient's quality of life. Neuropathic pain patients frequently experience severe anxiety, depression and sleep deprivation compared to chronic non-neuropathic pain patients (Smith & Torrance, 2012). It is estimated that around 31.7% of the general population experienced chronic pain and 6.9% were presented with neuropathic pain symptoms (Bouhassira et al., 2008). Most importantly, it is recorded that 7% of 30,000 Malaysian adults were presented with neuropathic pain symptoms (Cardosa et al., 2008). Based on Malaysia's chronic pain patient's latest data, it is reported that 5.4% of Malaysian diabetes mellitus patients were suffered from neuropathic pain (Li-Ying et al., 2017).

Compared to the other type of pain, chronic neuropathic pain is more complicated and undertreated due to the complexity and wide-ranging mechanisms involved (Rosenberger et al., 2020). Clinically, neuropathic pain signs and symptoms include sensory loss, spontaneous pain, hypersensitivity such as allodynia and hyperalgesia (stimulus evoke pain) (Jensen & Finnerup, 2014). Pharmacological treatment guidelines of neuropathic pain have highlighted the use of several types of medication, including antidepressants, anticonvulsants and opioid drugs for neuropathic pain treatment (O'Connor & Dworkin, 2009). The latter finding suggests that the combination of analgesic drugs acting through different mechanisms produces improved pain relief with fewer side effects (Gilron & Max, 2005; Kerstman et al., 2013).

Although neuropathic pain studies are increasing, many neuropathic pain patients do not significantly benefit from the pharmacological drug. The treatment of neuropathic pain has become more challenging because of the variability of the patient's clinical expression and sensory profile following the nerve injury (Bouhassira & Attal, 2016). The main critical problems with the current treatment are inadequate pain relief, probably

due to the insufficient knowledge of the pathophysiology mechanism of neuropathic pain and limited therapeutic capabilities of current treatment that accompanied by unfavourable short and long-term side effects (Bouhassira & Attal, 2019; Mendlik & Uritsky, 2015a; Moisset et al., 2020). Thus, neuropathies continue to challenge medical treatment and scientific research (Saade & Jabbur, 2008). Due to the increasing ageing population and several other factors, it is expected that the neuropathic pain incident will be increasing worldwide. Thus, research on a novel compound with lesser side effects and high efficacy as neuropathic pain medication is necessary.

Over the past half-century, the development of combinatorial chemistries and high-throughput screening procedures has contributed to the diversity of numerous synthetic drug production. Despite that, the natural products and their associated structures remain essential pharmacopoeia elements (Ngo et al., 2013). Natural products have emerged as a crucial therapeutic resource in developing new drugs for chronic pain treatment due to the fewer side effects produced and high efficacy in delivering the compound to the target site (Harvey et al., 2015; Quintans et al., 2014). Statistically, China and India recorded the highest medicinal plant usage in Asia with 11,146 and 7,500 species. In Malaysia, it is reported about 1,200 or 7% of the plant species were used for medicinal purposes (Alsarhan et al., 2014; Chen et al., 2016).

Chalcones is a naturally occurring compound that has garnered much interest among researchers due to its wide-ranging biological activities (Zhuang et al., 2017). The aromatic enone in chalcone belongs to the flavonoid family, which accounts for the plants' yellow pigmentation (Moreira et al., 2014). They are located in different plant regions, including the petal, fruits, leaves, heartwood, bark, and root of the plant. Thousand-year before, chalcones have been used to treat different medical disorders such as cancer, inflammation and diabetes (Batovska & Todorova, 2010; Zhou & Xing, 2015). One of the most important chalcones is cardamonin. Though it can be found in many other plant species, cardamonin is frequently assumed to be derived from cardamom. An innumerable amount of studies has demonstrated this compound's therapeutic properties to many pathological conditions, including inflammation, nociceptive and cancer. Most importantly, cardamonin is observed to exhibit potent analgesic properties in acute and chronic pain animal models (Ping et al., 2018; Sambasevam et al., 2017).

Pathophysiology underlying neuropathic pain is mainly due to the central and peripheral sensitisation upon nerve injury (Baron et al., 2010). With this basis, many research has been conducted to apprehend the neuropathic pain's pathophysiology further. Deleterious changes within the injured nerve along the central nervous system's nociceptive and modulatory pathways are among the pathophysiological of neuropathic pain (Cohen & Mao, 2014). Additionally, the descending modulation pathway, which is mainly controlled by serotonergic and noradrenergic neurons, is also implicated in neuropathic pain. Both neurons act synergistically in inhibiting nociceptive transmission (Jones et al., 2006). In the past few years, the serotonergic and noradrenergic system has become a target by natural products to exert a strong analgesic effect in neuropathic pain disorder (Chia et al., 2020; Kwon et al., 2014; Zhao et al., 2012). In fact, there are few serotonergic and noradrenergic receptors such as 5-HT_{1A} and α_{2A} are proven to alleviate nociceptive effect might be contributed by modulating the descending inhibition pathways in supraspinal and spinal region. Thus, identifying the underlying pathophysiology of

neuropathic pain development and the mechanism of action of the compound involved is necessary to elucidate further a more effective analgesic and precise treatment for a specific disorder.

Problem statement and justification of the study

Neuropathic pain patient is normally subject to the symptoms that range from numbness to the debilitating pain (Brooks & Kessler, 2017). The continuous symptoms onset is greatly affecting the patient's quality of life. Chronic neuropathic pain patient possesses higher degrees of anxiety and depression scores, as well as sleep disturbance compared to the chronic non-neuropathic pain patient. Numerous guidelines and consensus statements from various organisations around the world appear to be consistent with the classes of medications recommended for general and specific types of neuropathic pain, which include antidepressants and anticonvulsants. Even with the evidence-based treatment, the current drug regime still does not provide satisfactory pain relief to the patients. In some cases, the patient could not tolerate to the effective doses of the treatment due to the adverse effect (Brooks & Kessler, 2017). Additionally, prescription of the tricyclic antidepressant (TCA) to chronic pain patients with a history of cardiology disease can cause cardiac toxicity (Zapalska-Pozarowska et al., 2012). Thus, it is necessary to identify and explore a new novel compound that can replace the current treatment while providing added value to the drug development process.

Previously, our pilot study has evaluated the potential of cardamonin as a new compound that effective to alleviate neuropathic pain symptoms. The preclinical data on cardamonin shows their potency to alleviate hyperalgesia and allodynia in the CCI mice model with possible involvement of the opioidergic system (Sambasevam et al., 2017). Considering that descending pathways of pain involving different systems including opioidergic and monoaminergic, hence targeting and evaluating the involvement of these pathways can provide new updates and improvements to neuropathic pain treatment in future. Therefore, the current study hypothesised that cardamonin could alleviate hyperalgesia and allodynia in chronic constriction injury (CCI)-induced neuropathic pain mice model modulated via monoaminergic pathways. This study is crucial as it will provide in-depth information on cardamonin and its significance in neuropathic pain treatment.

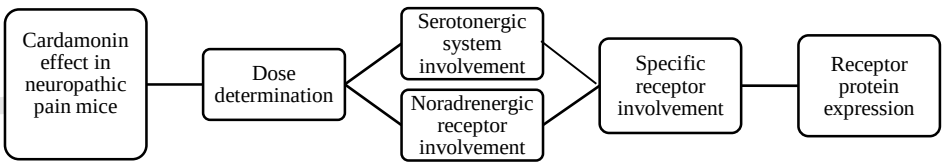

Figure 1: Conceptual framework of the project

Objectives of the Study

This study is generally conducted to investigate the effect of cardamonin in alleviating hyperalgesia and allodynia with the possible involvement of the monoaminergic system in the CCI-induced neuropathic pain mice model.

The specific objectives of the studies are as follows:

1. To determine the effective dose of cardamonin that can attenuate hyperalgesia and allodynia in the CCI-induced neuropathic pain mice model.

2. To investigate the participation of serotonergic systems in cardamonin-induced antihyperalgesic and antiallodynic in neuropathic pain mice model.

3. To determine serotonin receptor subtypes' contribution and the changes of 5-HT_{1A} expression in cardamonin-induced antihyperalgesic and antiallodynic in neuropathic pain mice model.

4. To investigate the participation of noradrenergic systems in cardamonin-induced antihyperalgesic and antiallodynic in neuropathic pain mice model.

5. To determine the noradrenergic receptor subtypes' contribution and the changes of α_{2A} expression cardamonin-induced antihyperalgesic and antiallodynic in the neuropathic pain mice model.

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