UNIVERSITI PUTRA MALAYSIA

ANTIHYPERALGESIC AND ANTI-ALLODYNIC PROPERTIES OF CARDAMONIN IN MICE MODEL OF NEUROPATHIC PAIN

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By

YOGESVARI SAMBASEVAM

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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DEDICATION

Every challenging work needs own great efforts and guidance, love as well as support from people who are very close to our heart.

I would like to dedicate my humble effort to my

Father & Mother
Mr Sambasevam Mukan & Mrs Santhi Muniandy

Husband
Mr Sharvieen Jaganathan

Brothers
Mr Balachandran Sambasevam, Mr ManiRajan Sambasevam & Mr Kurubaraneish Sambasevam

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

ANTIHYPERALGESIC AND ANTI-ALLODYNIC PROPERTIES OF CARDAMONIN IN MICE MODEL OF NEUROPATHIC PAIN

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May 2018

Chairman: Enoch Kumar Perimal, PhD
Faculty : Medicine and Health Sciences

Neuropathic pain is a chronic pain state caused by injury in the nervous system and often characterised by symptoms such as spontaneous pain, allodynia and hyperalgesia. Neuropathic pain is debilitating and highly resistant to current treatments such as nonsteroidal anti-inflammatory drugs (NSAIDS), anticonvulsants, antidepressants and opioids analgesics. Cardamonin is a naturally occurring chalcone. Studies have shown that cardamonin exhibited promising therapeutic effects such as antinociceptive and anti¨inflammatory. Importantly, cardamonin is able to reduce the production of inflammatory mediators that are also involved in the pathophysiology of neuropathic pain. The study was aimed to investigate the antihyperalgesic and anti-allodynic properties of cardamonin in CCI-induced neuropathic pain in mice and its possible mechanism of actions. Male ICR mice were used throughout the project. CCI-induced neuropathic pain model was performed. A small incision was made to expose the sciatic nerve on the left hind leg and loose ligatures were placed around the nerve. The neuropathic pain response was measured quantitatively by using Hargreaves Plantar test, dynamic plantar aesthesiometer test, cold plate test and Randall-Selitto test. Ligations study consisted of 5 groups of animals; sham-operated, 1-Ligation, 2-Ligations, 3-Ligations and 4-Ligations. Behavioural assessments were carried out for 12 weeks. Investigation of antihyperalgesic and anti-allodynic properties of cardamonin were carried out by treating animals exposed to CCI with vehicle (DMSO, Tween20, & distilled water), Amitriptyline (20 mg/kg) or cardamonin (3, 10 & 30 mg/kg) via intraperitoneal route. All treatments were administered for 7 days consecutively from day 15 till day 21 after surgery. Behavioural assessments were carried out on day 0, 14 (before treatment & after treatment) and 21. Mechanisms of actions (MOA) that were investigated in this project were the involvement of opioid receptors, L-arginine-nitric oxide/cGMP/ATP-sensitive K^+ channel pathway and potassium channels. Animals exposed with CCI were pre-treated with antagonists before the administration of cardamonin or vehicle. Behavioural tests were conducted after the administration of their respective treatments. Brain samples were collected to study the expression of opioid receptors via Western blotting. All

data were collected and expressed as mean ± SEM and were statistically analysed by using one-way Analysis of Variance (ANOVA), followed by Tukey's post-hoc test. The results were considered significant at $p<0.05$. Cardamonin (3, 10 & 30 mg/kg) exhibited antihyperalgesic and anti-allodynic activities on CCI-induced neuropathic pain model in mice. Cardamonin elicited its analgesic effects by activating L-arginine/cGMP/K^+-ATP channel pathway, opening the potassium channels as well as modulating pain signal via activation of delta- and kappa-opioid receptors. Modulation by these pathways and ion channels suppressed the neuronal hyperexcitability that arised due to peripheral nerve injury, hence producing analgesic effects. Taken together, cardamonin has the potential to be developed as a drug candidate for management of pain.

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

CIRI-CIRI ANTIHIPERALGESIK DAN ANTI-ALODINIK CARDAMONIN PADA MODEL KESAKITAN NEUROPATIK MENCIT

Oleh

YOGESVARI SAMBASEVAM

Mei 2018

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Kesakitan neuropatik adalah keadaan sakit kronik yang disebabkan oleh kecederaan dalam sistem saraf dan sering dicirikan oleh gejala seperti kesakitan spontan, alodinia dan hiperalgesia. Kesakitan neuropatik adalah melemahkan dan kesakitannya tidak reda apabila dirawat oleh ubat-ubatan seperti anti-radang bukan steroid (NSAIDS), antikonvulsif, antitekanan dan analgesik opioid. Cardamonin adalah kalkon yang terjadi secara semulajadi. Kajian telah menunjukkan bahawa cardamonin mempamerkan kesan terapeutik yang berkesan seperti antikesakitan dan antiradang. Yang penting, Cardamonin dapat mengurangkan pengeluaran mediator peradangan yang juga terlibat dalam patofisiologi kesakitan neuropatik. Kajian ini bertujuan untuk mengkaji sifat antihiperalgesik dan anti-alodinik cardamonin pada kesakitan neuropatik dalam model CCI tikus dan mekanisma tindakan yang terlibat. Tikus jantan ICR telah digunakan sepanjang projek ini. Model kesakitan neuropatik yang disebabkan oleh CCI telah digunakan. Insisi kecil dibuat untuk mendedahkan saraf skiatik di anggota belakang sebelah kiri dan ligatur longgar diletakkan di sekitar saraf. Tindak balas kesakitan neuropatik diukur secara kuantitatif dengan menggunakan ujian “Hargreaves Plantar”, ujian plantar aesthesiometer dinamik, ujian plat dingin dan ujian “Randall-Selitto”. Kajian ligasi terdiri daripada 5 kumpulan haiwan; sham, 1-Ligasi, 2-Ligasi, 3-Ligasi and 4-Ligasi. Penilaian tingkah laku dijalankan selama 12 minggu. Penyiasatan sifat antihiperalgesik dan anti-alodinik cardamonin dilakukan dengan merawat haiwan yang terdedah kepada CCI dengan “vehicle” (DMSO, Tween20 dan air suling), Amitriptyline (20 mg / kg) atau cardamonin (3, 10 & 30 mg/kg) secara intraperitoneal. Semua rawatan ditadbir selama 7 hari berturut-turut dari hari ke 15 hingga hari ke 21 selepas pembedahan. Penilaian terhadap kelakuan dijalankan pada hari 0, 14 (sebelum rawatan & selepas rawatan) dan 21. Mekanisme tindakan yang disiasat dalam projek ini adalah penglibatan reseptor opioid, laluan L-arginine-nitrik oxida dan saluran kalium. Haiwan yang terdedah dengan CCI sebelum ini dirawat dengan antagonis sebelum suntikan cardamonin. Ujian kelakuan dijalankan selepas rawatan. Sampel otak dikumpulkan untuk mengkaji ekspresi reseptor opioid melalui “Western blotting”. Semua data

dikumpulkan dan dinyatakan sebagai purata ± SEM dan dianalisis secara statistik dengan menggunakan Analisa Variasi satu arah (ANOVA), diikuti dengan ujian perbandingan pelbagai Tukey. Hasilnya dianggap signifikan pada $p < 0.05$. Cardamonin (3, 10 & 30 mg / kg) mempamerkan aktiviti antihiperalgesik dan anti-alodinik pada model sakit neuropatik yang disebabkan oleh CCI pada tikus. Cardamonin menimbulkan kesan analgesiknya dengan mengaktifkan saluran L-arginine / cGMP / K^+-ATP, membuka saluran kalium serta memodulasi isyarat sakit melalui pengaktifan reseptor delta dan kappa-opioid. Modulasi oleh saluran dan saluran ion ini akan memulihkan saraf yang terangsang seara luar biasa akibat kecederaan saraf periferal, dengan itu menghasilkan kesan analgesik. Kesimpulannya, cardamonin berpotensi untuk menjadi calon ubat yang efektif untuk pengurusan sakit kronik seperti neuropatik.

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I certify that a Thesis Examination Committee has met on 17 May 2018 to conduct the final examination of Yogesvari a/p Sambasevam on her thesis entitled "Antihyperalgesic and Antiallodynic Properties of Cardamonin in Mice Model of Neuropathic Pain" 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 are as follows:

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LIST OF ABBREVIATIONS

CNS	Central nervous system
NGF	Nerve growth factor
cAMP	Cyclic adenosine monophosphate
MAPK	Mitogen-activated protein kinase
TRPV	Transient receptor potential vanilloid
DRG	Dorsal root ganglion
NMDA	N-methyl-D-aspartic acid
CGRP	Calcitonin-gene related peptide
GABA	Gamma-aminobutyric acid
PAG	Periaqueductal gray
RVM	Rostral ventral medulla
TCA	Tricyclic antidepressants
SNI	Spared nerve injury
PSNL	Partial sciatic nerve ligation
SNL	Spinal nerve ligation
CCI	Chronic constriction injury
NO	Nitric oxide
NOS	Nitric oxide synthase
nNOS	Neuronal nitric oxide synthase
eNOS	Endothelial nitric oxide synthase
iNOS	Inducible nitric oxide synthase
cGMP	Cyclic guanosine monophosphate
K^+	Potassium ion

K_v	Voltage-gated potassium channel
Ca^{2+}	Calcium ion
BK_{Ca}	Large conductance calcium-activated potassium channel
SK_{Ca}	Small conductance calcium-activated potassium channel
NRM	Nuclues raphe magnus
COX-2	Cyclooxygenase-2
TNF-α	Tumor necrosis factor α
IL-1β	Interleukin 1β
IL-6	Interleukin 6
NF-κB	Nuclear factor kappa B
PGE_2	Prostaglandin E2
sGC	Soluble guanylyl cyclase

CHAPTER 1

INTRODUCTION

Chronic pain is a critical health issues and it is a great challenge of currently available medicines to provide complete pain relief to the patients in clinical settings (Nguelefack et al., 2010). Chronic pain can be grouped as nociceptive pain, sensory hypersensitivity and neuropathic pain, in relation to their respective underlying pathobiology (McCarberg et al., 2017). Nociceptive pain does not involve damage or dysfunction of the nervous system. However, it is concomitant with tissue damage due to trauma or inflammation (IASP, 2012). Sensory hypersensitivity is the amplification of sensory signal and lowering of pain threshold, due to prolong dysfunction of nervous system and does not involve any tissue or nerve damage (Petersel et al., 2011; Woolf, 2011). In contrast, neuropathic pain is the pain that arises due to direct impairment that takes place in the nervous system (Treede et al., 2008).

Millions of people worldwide are suffering from neuropathic pain that could give distressing impact to their quality of life as well as engaging in daily routines (Hall et al., 2006). Signs and symptoms such as hyperalgesia, allodynia are strongly characterised with neuropathic pain (Bridges et al., 2001). The prevalence of neuropathic pain has been evaluated to be in the range of 7-10% according to the studies carried out on the general population (Bouhassira et al., 2008; Van Hecke et al., 2014). In Malaysia, Hospital Selayang pain clinic reported that 38.8% of patients had neuropathic pain (Othman et al., 2011). In addition, a primary care clinic located at University Malaya Medical Center found that 54.8% patients are present with chronic pain (Ambigapathy, 2010). Nationwide, the prevalence of chronic persistent pain was found to be 7.1% among 33,733 adults (Cardosa et al., 2008). Generally, patients suffering from diabetic neuropathy, HIV infection, stroke and amputations are closely associated with neuropathic pain conditions (Colloca et al., 2017).

Neuropathic pain is unfavourable and unmanageable due to its wide-ranging and complex mechanisms (Baron et al., 2010). Available drugs such as antidepressants like amitriptyline, nortriptyline, anticonvulsants such as gabapentin, carbamazepine and opioids such as morphine and tramadol have limited therapeutic capability in the management of the debilitating chronic pain (Baron et al., 2010; O'Connor et al., 2009). Besides, administration of these drugs often produces side effects such as nausea, constipation and addiction to the patients and this limits the usage for neuropathic pain management (Attal et al., 2010). Thus, this study is conducted to explore on a novel potential lead compound, which is able to exhibit potent analgesic effects towards chronic pain as well as producing lesser or no side effects upon consumption.

The use of natural products has been closely related to the application of traditional medicines since thousands years ago. The natural products consist of medicinal plants are commonly used for treating, curing and preventing from various diseases, is the primitive form of medical practice in mankind (Li et al., 2009). In addition, aspirin and morphine are the pronounced example of drugs derived from plants, which are being incorporated in chemical, pharmacological and clinical studies (Newman et al., 2012). Natural products and active components with fewer adverse effects are emerging as beneficial medicament resources for the evolution of new drugs in the pain management procedures. In fact, neuropathic pain conditions are still contributing to their fair share in the process of developing novel medicines (Butler, 2004; Li et al., 2011).

An enormous number of studies have been focused on chalcones, an aromatic enones belonging to the flavonoids family and often responsible for yellow pigmentation of the plants (K Sahu et al., 2012). Cardamonin, a name thought to be originated from cardamom spices, is one of the examples of naturally occurring chalcone found in various plant species (Krishna et al., 1973). Researchers claim that cardamonin is highly potential in exhibiting various medicinal properties (Gonçalves et al., 2014). Most importantly, it has been shown to exhibit anti-inflammatory (Israf et al., 2007) and anti-nociceptive (Park et al., 2014) properties in *in vivo* as well as *in vitro* models. It is known that inflammatory and nociception involves the peripheral and central sensitization, thus it is relevant to study the effect of cardamonin on neuropathic pain since it shares similar pathophysiology.

Problem statement and justification of present study

The present study is carried out to establish a safer and effective drug in pursuit of better neuropathic pain management. Currently available drugs in clinical settings prescribed for patients diagnosed with neuropthic pain symptoms, are often associated with adverse effects and ineffectiveness. An evidence-based approach and specific recommendation has been shown by randomized controlled trials carried out for treatment of neuropathic pain for the use of various mode of drugs such as anticonvulsants, tricyclic antidepressants, topical lidocaine, serotonin–norepinephrine reuptake inhibitors as well as opioids such as tramadol. Among these drugs, anti-convulsants such as gabapentin and opioids like morphine have been chosen as two of several first-line treatments options for neuropathic pain (Dworkin et al., 2007). However, the adverse effects associated with opioids are distressing. Patients treated with opioid analgesics tend to develop dependence, withdrawal, abuse and immunologic changes (Vallejo et al., 2004). Besides, it was found that the response towards these drugs is often insufficient.

Therefore, a reliable novel substitute is needed to solve this worldwide issue while adding value to the drug development process. This study was commenced to provide a preclinical data on investigating the potential of cardamonin as antihyperalgesic and anti-allodynic agent. Cardamonin has been extensively studied and has been proved to exhibit various medicinal benefits, importantly,

antinociceptive and anti-inflammatory activities. Thus, it is admissible that cardamonin could be one of the candidate for the treatment of neuropathic pain symptoms.

Hypothesis

Cardamonin may potentially exhibit antihyperalgesic and anti-allodynic effects in chronic constriction injury-induced neuropathic pain in mice via activation of L-arginine-cGMP-K^+-ATP channel pathway, other potassium channels and opioidergic system.

Objectives of the Study

The general objective of the study is to investigate the antihyperalgesic and anti-allodynic properties of cardamonin in chronic constriction injury (CCI)-induced neuropathic pain model of mice and its possible mechanism of actions.

The specific objectives were to:

i. compare the effects of different number of ligations in CCI model of neuropathic pain in mice
ii. investigate the effects of cardamonin in attenuating hyperalgesia and allodynia in chronic constriction injury model of neuropathic pain in mice
iii. investigate the involvement of L-arginine-nitric oxide-cGMP pathway in cardamonin-induced antihyperalgesic and anti-allodynic properties.
iv. investigate the involvement of potassium channels in cardamonin-induced antihyperalgesic and anti-allodynic properties
v. elucidate the involvement of opioidergic system in cardamonin-induced antihyperalgesic and anti-allodynic properties

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