UNIVERSITI PUTRA MALAYSIA

ANTI-ALLODYNIC AND ANTIHYPERALGESIC ACTIVITIES OF ZERUMBONE IN CHRONIC CONSTRICTION INJURY-INDUCED NEUROPATHIC PAIN AND ITS POSSIBLE MECHANISM OF ACTION

NURUL ATIQAH BINTI ZULAZMI

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By

NURUL ATIQAH BINTI ZULAZMI

Thesis submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirement for the degree of Master of Science

April 2016

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DEDICATION

WITH APPRECIATION AND RESPECT,

THIS THESIS IS DEDICATED

TO

MY PARENTS MR ZULAZMI RAZALI

& NOOR LIZA HUSSAIN AND MY FAMILY

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

The present study was conducted to investigate the potential of zerumbone, a bioactive sesquiterpene of *Zingiber zerumbet* (L) Smith (*Z. zerumbet*) in anti-allodynic and antihyperalgesic properties in neuropathic pain induced by chronic constriction injury (CCI) in mice. We used this model and demonstrated the comparison of different number of sciatic nerve ligation (1, 2, 3 and 4). The outcome revealed that a single ligation CCI animal model on the sciatic nerve is enough to mimic the symptoms of neuropathic pain such as hyperalgesia and allodynia with almost similar effect with the usual 4 ligations sciatic nerve in CCI animal model. Indeed, acute and repeated intra-peritoneal (i.p) administration (on 14th day and continued administration once daily for 7 days) of zerumbone (10, 50, 100 mg/kg) significantly exhibited dose-dependent inhibition of chronic constriction injury induced-neuropathic pain in mice, when evaluated using von Frey filament test, cold plate, Randall-Selitto and Hargreaves plantar test ($p<0.05$). The compound was found to exert anti-allodynic and antihyperalgesic properties in chronic constriction injury (CCI) model and the optimum dose for zerumbone was found out to be 10 mg/kg. The anti-allodynic and antihyperalgesic effect of zerumbone (10 mg/kg i.p) were also significantly reversed by pre-treatment of L-arginine (10 mg/kg), 1H [1,2,4] Oxadiazole [4,3a] quinoxalin-1-one (ODQ), soluble guanosyl cyclase blocker (2 mg/kg i.p) and glibenclamide (ATP-sensitive potassium channel blocker) (10 mg/kg i.p). In addition, the histology of nerve morphology also showed a profound attenuation of mast cells around nerve fibres after treated 7 days daily with 10 mg/kg i.p and 50 mg/kg i.p of zerumbone ($p<0.05$). Even though, zerumbone failed to produce significant result with vehicle-treated group on the swelling of nerve fibre but the anti-inflammatory effect of zerumbone was able to attenuate the inflammatory cells surrounding the nerve fibre. Together, these findings proved that zerumbone produce pronounced anti-allodynic and antihyperalgesic effects in modified CCI model of neuropathic pain in mice that involves inhibition of L-arginine-NO-Cyclic GMP (cGMP) pathway followed by the opening of ATP-sensitive K+ channel at the peripheral level. Hence, considering that few effective drugs that are available in the market for the treatment of neuropathic pain, this study indicates that zerumbone a potentially interesting in the development of new clinically relevant drugs for the management of chronic pain.

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

AKTIVITI ANTI-ALODINIK DAN ANTIHIPERALGESIK ZERUMBONE TERHADAP KECEDERAAN PENYEMPITAN KRONIK YANG MENYEBABKAN KESAKITAN SARAF DAN MEKANISMA DISEBALIKNYA.

Oleh

NURUL ATIQAH BINTI ZULAZMI

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Kajian ini dijalankan bagi menunjukkan potensi zerumbone sebagai bahan bioaktif *Zingiber zerumbet* (L) Smith (*Z. zerumbet*) dalam menghasilkan kesan anti-alodinik dan antihiperalgesik terhadap sakit neuropatik yang dipengaruhi oleh model haiwan dengan konstriksi saraf yang kronik (CCI). Beberapa bilangan ikatan (1,2,3 dan 4) pada bahagian saraf siatik telah dihasilkan bagi memilih model CCI yang terbaik dan satu ikatan saraf siatik telah berjaya menghasilkan kesakitan neuropatik yang sama seperti dihasilkan oleh empat bilangan ikatan saraf siatik iaitu ikatan sebenar model haiwan CCI sebelum ini. Penemuan ini diteruskan dengan memberi rawatan zerumbone kepada model CCI yang terpilih. Suntikan akut intra-peritoneal dan berulang kali (pada hari ke-14 dan suntikan berturutan selama 7 hari) zerumbone (10, 50, 100 mg/kg) menghasilkan kesan perencatan bersandar dos terhadap CCI apabila dinilai menggunakan von Frey Ujian Filamen, Plantar Sejuk, Randall-Selitto, dan Ujian Plantar Hargreaves ($p<0.05$). Zerumbone ternyata memberi kesan anti-alodinik dan antihiperalgesik terhadap model CCI. Manakala, dos terbaik zerumbone yang memberikan kesan optimum ialah 10 mg/kg. Kesan anti-alodinik dan antihiperalgesik zerumbone (10 mg/kg ip) telah dibalikkan dengan suntikan pra-rawatan L-arginina (10 mg/kg), *1H [1, 2, 4] Oxadiazole [4,3a] quinoxalin-1-one* (ODQ) (penyekat Guanosil Siklase) (2 mg/kg ip) dan *Glibenclamide* (penyekat saluran kalium) (10 mg/kg ip). Manakala, data terhadap histologi morfologi saraf juga menunjukkan pengurangan bilangan sel mast di gentian saraf akibat CCI apabila dirawat selama 7 hari dengan 10 mg/kg ip dan 50 mg/ kg ip zerumbone ($p<0.05$). Walaubagaimanapun, zerumbone gagal membaiki struktur saraf tetapi kesan anti-radang zerumbone telah berjaya menghapuskan sel-sel radang sekitar gentian saraf. Kesimpulannya, penemuan ini telah membuktikan bahawa zerumbone menghasilkan kesan anti-alodinik dan antihiperalgesik yang ketara dalam model CCI yang menyebabkan kesakitan neuropatik melalui penglibatan laluan L-arginina-NO-Cyclic GMP (cGMP) yang diikuti oleh pembukaan saluran ATP sensitif K^+ pada peringkat periferi. Oleh itu, memandangkan hanya beberapa ubat berkesan yang terdapat di pasaran bagi merawat kesakitan neuropatik, kajian aktiviti zerumbone telah membuktikan bahawa zerumbone mungkin berpotensi dalam pembangunan ubat-ubatan klinikal yang baru untuk pengurusan sakit kronik ini.

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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 Master of Science. The members of the Supervisory Committee were as follows:

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LIST OF ABBREVIATIONS

IASP	International Association Study of Pain
nNOS	Neuronal nitric-oxide synthases
iNOS	Inducible nitric-oxide synthases
cGMP	central guanosine 3,5 -cyclic monophosphate
PKG	protein kinase G
sGC	soluble guanylate cyclase
K^{+ATP}	ATP-sensitive potassium
CCI	Chronic Constriction Injury
RZZ	*Zingiber zerumbet*
HTC	Hepatoma Tissue Culture
PNS	peripheral nervous system
CNS	central nervous system
NGF	nerve growth factor
NMDA	N-methyl-D-aspartate
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
IUPAC	International Union of Pure and Applied Chemistry
GABA	Gamma-aminobutyric acid
NO	Nitric Oxide
NOS	Nitric Oxide Synthase
PKC	Protein Kinase C
DMSO	dimethylsulfoxide
ANOVA	one way analysis variance
L-NOARG	L-NG-nitro arginine
L-arginine	L-arginine hydrochloride
ODQ	Oxadiazole [4, 3-a] quinoxaline-1-one
NaCl	Sodium Chloride
H&E	Hematoxylin and Eosin
MCP-1	monocyte chemoattractant protein-1

CHAPTER 1

INTRODUCTION

1.1 Neuropathic pain

Neuropathic pain has become a common issue that affected millions of people around the world (Tsuda *et al.,* 2005). Apart from that, The Ministry of Health Malaysia in the Quick Reference Guide on Management of Cancer Pain, 2010 classified neuropathic pain as a difficult type of pain syndrome that is critically in need of adjuvant analgesics and additional interventions. International Association Study of Pain (IASP) defined neuropathic pain as a pain that is caused by a lesion or disease on the somatosensory system. Nevertheless, this type of pain is often associated with disease or injury to the peripheral and central nervous system that usually causes abnormal processing of sensory input (Jensen *et al.,* 2001; Dworkin *et al.,* 2003).

Neuropathic pain is categorized as a pathophysiologic pain which is dissimilar from physiologic pain in many ways and this includes the mechanism that is underlying it (Iyengar *et al.,* 2004; Pasero, 2004). Additionally, neuropathic pain is described as constant pain arising from the changes that originate in pain sensory system after peripheral nerve injury (Iyengar *et al.,* 2004). Moreover, this pain can be indicated by the sensory impairment such as unpleasant abnormal sensation (dyesthesia), increase response to a normal painful stimulus (hyperalgesia) and pain that is caused by normal non-painful stimulus (allodynia) (Jaggi *et al.,* 2011). While other related symptoms include the altered pain sensation, numbness, burning and continuous or intermittent evoked or spontaneous pain (Ueda and Rashid, 2003).

However, existing treatment such as non-steroidal anti-inflammatory drugs (NSAIDs) and opiates showed little success with a limited response in neuropathic pain (Dowdall *et al.,* 2005). Plus, the commonly used medications for neuropathic pain also cause numerous side effects, unpredictable effectiveness, complex doses, delayed analgesic onset and somehow can reduce the patient's quality of life (Meyer-Rosberg *et al.,* 2001; Dworkin *et al.,* 2007). Although, the mechanisms of neuropathic pain are not yet fully understood, substances that have potential inhibitory effect on this type of pain with minimal or no adverse effect are of analgesic research interest.

1.2 Current Research Interest

Complications and problems that arise perpetuate a clear of unmet therapeutic needs and a high demand for the field of drug discovery (Gutierrez *et al.,* 2012). In conjunction with that, herbal medicines and alternative medicine has been used by the general population today because of dissatisfaction on ineffective conventional treatment and their adverse effects (Astin, 1998). *Zingiber zerumbet* is considered as a large genus of herbs that belongs to the family of Zingiberaceae. This species consist

about 141 species that is scattered mainly in Asia and confined to the tropics in Asia, Malaysia and Pacific Islands (Burkill, 1966; Jantan *et al.,* 2003). The name 'lempoyang' were given by Malaysians and Indonesians and this plant has also been traditionally used as folkoric medicine (Habsah *et al.,* 2000).

Zerumbone is a bioactive sesquiterpene that is found to be one of the major components in the rhizome of *Zingiber zerumbet* Smith (Sulaiman *et al.,* 2010b) that has been studied extensively in in-vivo and in-vitro studies (Yob *et al.,* 2011). Surprisingly, there are some medicinal properties that has been previously reported for zerumbone such as antinociceptive (Perimal *et al.,* 2011), anti-inflammatory (Sulaiman *et al.,* 2010a) and antitumor activities (Murakami *et al.,* 2004; Huang *et al.,* 2005). Even though, several researchers potrayed some information about the capabilities of zerumbone with pathways underlying physiological pain, but still no research has discussed its effects on neuropathic pain and the mechanism behind it.

One of the important pathways associated with neuropathic pain mechanism is the L-arginine-nitric oxide-cGMP-K^+ATP pathway. Nitric oxide is synthesized by neuronal (nNOS) or inducible (iNOS) nitric-oxide synthases via central guanosine 3,5 -cyclic monophosphate (cGMP)-protein kinase G (PKG) pathway activation that mediates numerous neuropathic pain symptoms (Meller *et al.,* 1992). Ionic channel modulation by NO can be produced either indirectly through the classical pathway of soluble guanylate cyclase (sGC) activation and generation of cGMP, or directly through a pathway involving S-nitrosylation of target proteins (Ahern *et al.,* 2002). Nonetheless, pharmacological studies in vivo imply that K^+ATP channels in peripheral sensory neurons may be activated indirectly via the NO/cGMP/PKG pathway (Soares and Duarte, 2001; Alves *et al.,* 2004a; Sachs *et al.,* 2004) . Some drugs produce peripheral analgesia via NO-dependent activation of ATP-sensitive potassium (K^+ATP) channels (Rodrigues and Duarte, 2000; Lázaro-Ibáñez *et al.,* 2001; Granados-Soto *et al.,* 2002; Alves *et al.,* 2004b). Therefore, this study attempted to illustrate the effects of zerumbone towards neuropathic pain on the neuropathic animal model and provide better understanding of some mechanism of action underlying it.

1.3 Objectives

General objective:

This research was conducted to investigate the anti-allodynic and antihyperalgesic effects of zerumbone in an animal model of neuropathic pain.

Specific objectives:

i) To investigate and compare the pain developed by number of different sciatic nerve ligations in Chronic Constriction Injury (CCI) animal model of neuropathic pain as a pilot study.

ii) To evaluate the anti-allodynic and antihyperalgesic effects of different doses of zerumbone in tactile, thermal and mechanical test in animal model of neuropathic pain.

iii) To elucidate the role of L-Arginine-NO-cGMP-K^+ATP channel pathway in the zerumbone analgesic activities in vivo.

iv) To assess the effect of zerumbone treatment on the sciatic nerve morphology.

1.4 Hypothesis

Zerumbone significantly inhibits the allodynia and hyperalgesia caused by CCI animal model of neuropathic pain.

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