UNIVERSITI PUTRA MALAYSIA

ANTI-ALLODYNIC AND ANTIHYPERALGESIC PROPERTIES OF ZERUMBONE AND THEIR MECHANISMS OF ACTION IN MICE MODEL OF NEUROPATHIC PAIN

BANULATA GOPALSAMY

FPSK(P) 2017 2

ANTI-ALLODYNIC AND ANTIHYPERALGESIC PROPERTIES OF ZERUMBONE AND THEIR MECHANISMS OF ACTION IN MICE MODEL OF NEUROPATHIC PAIN

By

BANULATA GOPALSAMY

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

April 2017

DEDICATION

To my mum who was taken away just too soon

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

ANTI-ALLODYNIC AND ANTIHYPERALGESIC PROPERTIES OF ZERUMBONE AND THEIR MECHANISMS OF ACTION IN MICE MODEL OF NEUROPATHIC PAIN

By

BANULATA GOPALSAMY

April 2017

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

Neuropathic pain is a chronic pain condition that affects almost 6-10% of the world population severely affecting their quality of life. To date, conventional drugs could not provide complete pain relief and therefore alternative treatments are rapidly sought after. Zerumbone, a compound isolated from *Zingiber zerumbet*, was reported to exhibit anti-inflammatory and antinociceptive properties and therefore will able to attenuate the symptoms of neuropathic pain. This study was carried out to evaluate the properties of zerumbone in a chronic constriction injury (CCI)-induced mice model of neuropathic pain. The first study was conducted to characterise the various neuropathic pain models developed with different number of ligations. The outcome showed that single ligation was sufficient to well-surrogate this model as the models with different number of ligations showed similar levels of allodynia, hyperalgesia, nerve degeneration and expressions of pain marker, c-*fos*. Following that, this study elucidated the anti-allodynic and antihyperalgesic properties of zerumbone at doses 10 and 50 mg/kg; i.p. However, at the optimal dose of 10 mg/kg, zerumbone did not show any distinct reduction in c-*fos* expression. However, zerumbone does not maintain the nerve integrity or delay the nerve degeneration process following nerve injury. Nevertheless, zerumbone successfully suppressed Interleukin (IL)-1β, IL-6, Tumor Necrosis Factor (TNF)-α but not IL-10 in blood plasma and spinal cord at doses 10 and 50mg/kg; i.p. The following study demonstrated that the action of zerumbone lasts for two hours upon both single and long-term repeated treatments. Furthermore, zerumbone was able to reduce stimulus-induced-c-*fos* expressions at the spinal cord, cingulate cortex and parafascicular nuclei regions of the brain indicating antinociceptive properties of zerumbone at specific sites. This study further supported the results by demonstrating the involvements of the opioidergic system, specifically the μ-, κ- and δ-opioid subtypes in the attenuation of allodynia and hyperalgesia by zerumbone. Moreover, the involvement of potassium (K^+) channels including the voltage gated K^+ channels (K_v), ATP-sensitive K^+ channels (K_{ATP}), small and large conductance calcium activated K^+ channels in zerumbone-induced analgesia has also been elucidated. In conclusion, zerumbone exhibits anti-allodynic, antihyperalgesic and anti-inflammatory properties providing evidence that zerumbone might be a potential lead compound for the treatment of neuropathic pain.

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

CIRI-CIRI ANTI-ALODINIK DAN ANTIHIPERALGESIK ZERUMBONE DAN MEKANISMA TINDAKAN DALAM MODEL MENCIT SAKIT NEUROPATIK

Oleh

BANULATA GOPALSAMY

April 2017

Pengerusi : Enoch Kumar Perimal, PhD
Fakulti : Perubatan dan Sains Kesihatan

Sakit neuropatik adalah kesakitan kronik yang menjejaskan hampir 6-10% populasi dunia dimana kualiti hidup mereka amat terjejas. Sehingga kini, ubat-ubatan konvensional tidak dapat memberi kelegaan yang menyeluruh dan oleh itu, rawatan alternatif dicari dengan cepat. Zerumbone, adalah sebatian yang diasingkan daripada *Zingiber* zerumbet, yang dilaporkan untuk ciri-ciri anti-inflammasi dan anti-nosiseptif, dan oleh itu mampu mengurangkan simtom-simptom kesakitan neuropatik. Kajian ini telah dilaksanakan untuk menilai ciri-ciri zerumbone dalam kecederaan penyempitan kronik yang diaruh pada model mencit untuk kesakitan neuropatik. Kajian pertama telah dijalankan untuk mencirikan pelbagai model kesakitan neuropatik yang dihasilkan dengan bilangan ligasi yang berlainan. Penilaian hasil kajian menunjukkan ligasi tunggal mampu menghasilkan model ini dengan baik kerana model-model lain dengan bilangan ligasi yang berbeza menunjukkan tahap yang sama bagi alodinia, hiperalgesia, degenerasi saraf, dan ekspresi penanda sakit, c-*fos*. Berikutan itu, kajian ini menjelaskan ciri-ciri anti-alodinik dan anti-hiperalgesik zerumbone pada dos 10 dan 50 mg/kg;i.p. Walaubagaimanapun, pada dos optimal, 10mg/kg, zerumbone tidak menunjukkan pengurangan ketara dalam ekspresi c-*fos*. Kajian tentang ciri-ciri pelindungan saraf oleh zerumbone menunjukkan bahawa zerumbone tidak dapat mengekalkan struktur saraf ataupun melengahkan proses degenerasi berikutan kecederaan saraf. Walaubagaimanapun, zerumbone berjaya mengurangkan perantara inflamasi Interleukin (IL) -1β, IL-6, Faktor Nekrosis Tumor (TNF)-α dan bukan IL-10 dalam plasma darah dan korda spina pada dos 10 dan 50mg/kg; i.p. Kajian seterusnya menunjukkan bahawa tindakan zerumbone berkesan selama dua jam berikutan rawatan tunggal dan juga rawatan berulang. Selain itu, zerumbone berjaya mengurangkan ekspresi-c-*fos* yang diinduksi oleh rangsangan pada korda spina, korteks singulat dan nukleus parafasikular dalam otak yang menunjukkan kesan anti-kesakitan zerumbone yang berlaku adalah pada kawasan spesifik. Kajian ini menyokong hasil kajian dengan menunjuakkan penglibatan sistem opiod, secara spesifiknya, μ-, κ- dan δ- subjenis opioid dalam pengurangan alodinia dan hiperalgesia oleh zerumbone. Lebih-lebih lagi, penglibatan saluran kalium (K^+) termasuk saluran K^+ voltan berpagar (K_v), saluran K^+ sensitif ATP (K_{ATP}), saluran K^+ kealiran kecil yang diaktifkan oleh kalsium (SK_{Ca}) dan

saluran K^+ kealiran besar yang diaktifkan oleh kalsium (BK_{Ca}) dalam analgesia yang diaruhkan oleh zerumbone telah dijelaskan. Kesimpulannya, zerumbone menunjukkan ciri-ciri anti-alodinik, antihiperalgesik dan anti-inflamasi, dan telah membuktikan bahawa zerumbone berpotensi untuk digunakan sebagai rawatan sakit neuropatik.

ACKNOWLEDGEMENTS

The entire journey of my PhD studies was a great and pleasurable one which would just not be possible without the involvement of many. My heartfelt gratitude goes to:

Dr Enoch - who did not only provided a perfect guidance through his wisdom, patience, understanding throughout but is also a great role model to me. I thank you for always pushing me further to strive for more than I could possibly have achieved.

Prof. Roslan and Dr. Akira - my co-supervisors, who provided insightful comments, ideas and suggestions on my project. I was immensely inspired by your wisdom and enthusiasm in sharing your knowledge and experiences with us.

Staffs of the Physiology Lab and Cell Signaling Lab of FPSK and the Microscopy Unit of IBS - for their assistance and help in providing me with the best facilities and services.

My lab mates, Jasmine, Pui Ping, Atiqah, Voon, Yoges, Sahba, Ming and others - who helped me survive this journey with so much of fun and filled it with great memories. Thank you for being there for me, especially during the times when I needed you the most.

My dearest friends, Menax, Krish, Mages, Nithiyaa, Hema and others for your unconditional love and support throughout my PhD studies.

My family, dad and sister – For their constant prayers, support and love. You are the greatest blessings in my life and the strength that kept me going.

Thank you to also to whomever that I have failed to mention here.

I certify that a Thesis Examination Committee has met on 28 April 2017 to conduct the final examination of Banulata a/p Gopalsamy on her thesis entitled "Anti-Allodynic and Antihyperalgesic Properties of Zerumbone and their Mechanisms of Action 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.

Members of the Thesis Examination Committee were as follows:

Cheah Yoke Kqueen, PhD
Associate Professor
Faculty of Medicine and Health Science
Universiti Putra Malaysia
(Chairman)

Mohamad Aris bin Mohd Moklas, PhD
Associate Professor
Faculty of Medicine and Health Science
Universiti Putra Malaysia
(Internal Examiner)

Rajesh a/l Ramasamy, PhD
Associate Professor
Faculty of Medicine and Health Science
Universiti Putra Malaysia
(Internal Examiner)

Ekkasit Kumarnsit, PhD
Assistant Professor
Prince of Songkla University
Thailand
(External Examiner)

NOR AINI AB. SHUKOR, PhD
Professor and Deputy Dean
School of Graduate Studies
Universiti Putra Malaysia

Date: 6 July 2017

This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfillment of the requirement for the degree of Doctor of Philosophy. The members of the Supervisory Committee were as follows:

Enoch Kumar Perimal, PhD
Senior Lecturer
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Chairman)

Mohd. Roslan Sulaiman, PhD
Professor
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Member)

Ahmad Akira Omar Farouk, PhD
Senior Lecturer
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Member)

ROBIAH BINTI YUNUS, PhD
Professor and Dean
School of Graduate Studies
Universiti Putra Malaysia

Date:

Declaration by graduate student

I hereby confirm that:

- this thesis is my original work;
- quotations, illustrations and citations have been duly referenced;
- this thesis has not been submitted previously or concurrently for any other degree at any other institutions;
- intellectual property from the thesis and copyright of thesis are fully-owned by Universiti Putra Malaysia, as according to the Universiti Putra Malaysia (Research) Rules 2012;
- written permission must be obtained from supervisor and the office of Deputy Vice-Chancellor (Research and Innovation) before thesis is published (in the form of written, printed or in electronic form) including books, journals, modules, proceedings, popular writings, seminar papers, manuscripts, posters, reports, lecture notes, learning modules or any other materials as stated in the Universiti Putra Malaysia (Research) Rules 2012;
- there is no plagiarism or data falsification/fabrication in the thesis, and scholarly integrity is upheld as according to the Universiti Putra Malaysia (Graduate Studies) Rules 2003 (Revision 2012-2013) and the Universiti Putra Malaysia (Research) Rules 2012. The thesis has undergone plagiarism detection software.

Signature: _____ Date: _____

Name and Matric No.: _Banulata Gopalsamy, GS38850_____

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.

Signature: _____
Name of Chairman of Supervisory Committee: _____

Signature: _____
Name of Member of Supervisory Committee: _____

Signature: _____
Name of Member of Supervisory Committee: _____

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

CCI	Chronic Constriction Injury
IL	Interleukin
TNF	Tumour Necrosis Factor
CC	Cingulate Cortex
PfN	Parafascicular Nuclei
AMG	Amygdala
HC	Hippocampus
SEM	Standard Error of Mean
ANOVA	Analysis of Variance
SPSS	Statistical Analysis for Social Science
ELISA	Enzyme Linked Immunosorbent Assay

CHAPTER 1

INTRODUCTION

Neuropathic pain has been defined as "the pain caused by a lesion or disease of the somatosensory nervous system" (IASP, 2012). Neuropathic pain could be from both the peripheral and central origin depending on the site of the lesion or disease (Ringkamp and Raja, 2014). This type of pain is often chronic and said to be complex due to the pathophysiological changes it could bring to the normal function and pathology of nerves. Nerves themselves are damaged causing incorrect signals to be transmitted to other pain centres (Campbell and Meyer, 2006).

Neuropathic pain is highly prevalent and is a global problem. An epidemiological study by van Hecke *et al*. (2014) estimated that around 6.9%-10% of the worldwide population are affected by neuropathic pain and is expected to rise in years to come. Nationwide, it was reported that almost half of the cases being treated for pain are with neuropathic characteristics. In order to highlight the seriousness of this problem, the year 2014-2015 has been announced as the "Global Year Against Neuropathic Pain" by the International Association for the Study of Pain (IASP, 2012).

There are various factors that contribute to neuropathic pain such as direct trauma, cancer or tumour compression to the nerve. Apart from that, chemotherapy drugs, poisons or toxins, alcohol, infection and inflammation could also give rise to this pain condition. Metabolic diseases such as diabetes is the commonest cause for peripheral neuropathy (Boulton *et al*., 2005) while hereditary involvement has been previously reported (Marchettini *et al*., 2006).

This pain condition could become rather unbearable which compromises all domains of the lives of those affected as their mobility and physical activities becomes largely limited, making them to be essentially dependent on others (Gore *et al*., 2005). The agonizing pain felt by patients leaves them in a rather depressive-state further causing emotional distress not only to the patients but also to their caretakers. Therefore, any approach with the promise of pain relief is rapidly sought after.

To date, there is a wide array of commercially available drugs as treatment to relief neuropathic pain. Patients with symptoms of neuropathic pain are started with first-line drugs such as tricyclic antidepressants, topical antineuralgics, analgesics and antiepileptic drugs. Second- and third-line drugs are prescribed only when all first-line drugs options have been exhausted (Namaka *et al*., 2004). Other examples of drug to treat this pain condition include opioids, selective serotonin norepinephrine reuptake inhibitors, non-steroidal anti-inflammatory drugs (NSAIDS), topical anaesthetic agents and non-narcotic analgesics (Chen *et al*., 2004). Furthermore, if patients respond weakly to monotherapy, a combination of therapies will be prescribed. Only cases which are totally refractory to all forms of pharmacotherapy are referred to pain clinics, which will then involve a more invasive approach such as surgery (Namaka *et al*.,

2004). Other approaches include neuromodulation which are carried out in clinical practises in three methods; peripheral nerve field stimulation, peripheral nerve stimulation and percutaneous electrical nerve stimulation. The method typically involves giving an alternate electrical stimulation throughout a prefixed period of time, through the skin at the painful area by inserting a fine gauge needle (Alo *et al*., 2011).

However, several challenges are encountered when these currently available medications are employed to patients. The medications are often only partially effective and are not able to provide complete pain relief (Gwynn, 2015). They are also often accompanied with various adverse effects while some medications could be costly and not readily available (O'Connor, 2009). In some cases which require long-term chronic treatment, it leads to several other health complications. For example, long term opioid treatment could lead to sedative effects, addiction, physical dependence or cause the development of tolerance. Furthermore, patients could also exhibit severe withdrawal effects (Rosenblum *et al*., 2008).

Undesired consequences of these treatments necessitate the need to find other alternatives or potent analgesic compounds with fewer side effects. In that attempt, the use of natural products or herbs with medicinal properties seemed like a promising option as it has been traditionally used since our ancestry times. Traditional or folkloric medicines are longstanding remedies which has been passed on and developed over generations. Traditional medicine is defined by The World Health Organisation as "the sum total of the knowledge, skills, and practices based on the theories, beliefs, and experiences indigenous to different cultures, whether explicable or not, used in the maintenance of health as well as in the prevention, diagnosis, improvement or treatment of physical and mental illness" (WHO, 2008).

Ginger, one of the commonly used natural products in traditional medicine, is now gaining popularity in pharmaceutical industries due to its broad range of health benefits. *Zingiber zerumbet*, known as "lempoyang" in the Malay language which belongs to the Zingiberaceae family has been of great research interest. This ginger plant, commonly found in the tropical and subtropical regions, has been demonstrated to possess phytochemicals that is of high medicinal values (Jang and Seo, 2005).

Zerumbone is a compound that was isolated from the essential oil of the rhizomes of *Zingiber zerumbet* in the year 1956 (Dev, 1960). Ever since, zerumbone has been under scrutiny for various medicinal properties. A large body of literature has documented the properties of zerumbone, where this compound possess anticonvulsant (Yob *et al*., 2011), anti-oxidant (Sidahmed *et al*., 2015), anticancer (Kapoor, 2012), antidiabetic (Tzeng *et al*., 2013) and most importantly anti-inflammatory (Somchit *et al*., 2012;Sulaiman *et al*., 2010), antinociceptive and analgesic (Sulaiman *et al*., 2009;Perimal *et al*., 2011) properties.

Noting that the pain exhibited in neuropathic condition is largely mediated by the inflammatory process, zerumbone's anti-inflammatory and antinociceptive properties might be of advantage. To date, there is no scientific evidence on the testing of

zerumbone on a neuropathic pain model. Due to its vast medicinal properties, zerumbone is a potential lead for scientific evaluations on its potent analgesic effect. Therefore, it is hypothesised that zerumbone is able to attenuate allodynia and hyperalgesia via the involvement of opioid receptors and potassium channels.

Objectives of this study

The general objectives of this study are to investigate the anti-allodynic and antihyperalgesic effect of zerumbone and its possible mechanisms of action on mice model of neuropathic pain.

The specific objectives of this study are to:

1. characterise the chronic constriction injury model of neuropathic pain
2. investigate the anti-allodynic and antihyperalgesic properties of zerumbone, c-*fos* expression in the spinal and supraspinal regions in zerumbone-induced analgesia and the time course of its effect
3. elucidate the involvement of opioid receptors and potassium channels in zerumbone-induced analgesia
4. investigate the nerve structure integrity and anti-inflammatory properties following zerumbone treatment

REFERENCES

Abdelwahab, S. I., Abdul, A. B., Devi, N., Taha, M. M. E., Al-Zubairi, A. S., Mohan, S. & Mariod, A. A. 2010. Regression of cervical intraepithelial neoplasia by zerumbone in female Balb/c mice prenatally exposed to diethylstilboestrol: involvement of mitochondria-regulated apoptosis. *Experimental and Toxicologic Pathology,* 62**,** 461-469.

Abdelwahab, S. I., Abdul, A. B., Zain, Z. N. M. & Hadi, A. H. A. 2012. Zerumbone inhibits interleukin-6 and induces apoptosis and cell cycle arrest in ovarian and cervical cancer cells. *International Immunopharmacology,* 12**,** 594-602.

Aceto, M. D., May, E. L., Harris, L. S., Bowman, E. R. & Cook, C. D. 2007. Pharmacological studies with a nonpeptidic, delta-opioid (-)-(1R,5R,9R)-5,9-dimethyl-2'-hydroxy-2-(6-hydroxyhexyl)-6,7-benzomorphan hydrochloride ((-)-NIH 11082). *European Journal of Pharmacology,* 566**,** 88-93.

Acevedo, J. C., Amaya, A., Casasola, O. D. L., Chinchilla, N., De Giorgis, M., Flórez, S., Genis, M. Á., Gómez-Barrios, J. V., Hernández, J. J., Ibarra, E., Moreno, C., Orrillo, E., Pasternak, D., Romero, S., Vallejo, M., Velasco, M. & Villalobos, A. 2009. Guidelines for the Diagnosis and Management of Neuropathic Pain: Consensus of a Group of Latin American Experts. *Journal of Pain & Palliative Care Pharmacotherapy,* 23**,** 261-281.

Adelman, J. P., Maylie, J. & Sah, P. 2012. Small-conductance Ca2+-activated K+ channels: form and function. *Annual Review of Physiology,* 74**,** 245-269.

Al-Amin, M., Sultana, G. N. N. & Hossain, C. F. 2012. Antiulcer principle from Zingiber montanum. *Journal of Ethnopharmacology,* 141**,** 57-60.

Al-Hasani, R. & Bruchas, M. R. 2011. Molecular Mechanisms of Opioid Receptor-Dependent Signaling and Behavior. *Anesthesiology,* 115**,** 1363-1381.

Al-Saffar, F. J., Ganabadi, S., Fakurazi, S. & Yaakub, H. 2011. Zerumbone significantly improved immunoreactivity in the synovium compared to Channa striatus extract inmonosodium iodoacetate (MIA)-induced knee osteoarthritis in rat. *Journal of Medicinal Plants Research,* 5**,** 1701-1710.

Al-Saffar, F. J., Ganabadi, S., Fakurazi, S., Yaakub, H. & Lip, M. 2010. Chondroprotective effect of zerumbone on monosodium iodoacetate induced osteoarthritis in rats. *Journal of Applied Sciences,* 10**,** 248-260.

Al-Zubairi, A. S., Abdul, A. B., Yousif, M., Abdelwahab, S. I., Elhassan Taha, M. M. & Mohan, S. M. 2010. In vivo and in vitro genotoxic effects of zerumbone. *Caryologia,* 63**,** 11-17.

Ali, B. H., Blunden, G., Tanira, M. O. & Nemmar, A. 2008. Some phytochemical, pharmacological and toxicological properties of ginger (Zingiber officinale Roscoe): A review of recent research. *Food and Chemical Toxicology,* 46**,** 409-420.

Allchorne, A. J., Broom, D. C. & Woolf, C. J. 2005. Detection of cold pain, cold allodynia and cold hyperalgesia in freely behaving rats. *Molecular Pain,* 1**,** 36.

Almeida, T. F., Roizenblatt, S. & Tufik, S. 2004. Afferent pain pathways: a neuroanatomical review. *Brain Research,* 1000**,** 40-56.

Alo, K. M., Abramova, M. V. & Richter, E. O. 2011. Percutaneous peripheral nerve stimulation. *Prog Neurol Surg,* 24**,** 41-57.

Altier, C. & Zamponi, G. W. 2004. Targeting Ca2+ channels to treat pain: T-type versus N-type. *Trends in Pharmacological Sciences,* 25**,** 465-470.

Altman, R. D. & Marcussen, K. C. 2001. Effects of a ginger extract on knee pain in patients with osteoarthritis. *Arthritis & Rheumatology,* 44**,** 2531-2538.

Alves, D. P., Soares, A. C., Francischi, J. N., Castro, M. S., Perez, A. C. & Duarte, I. D. 2004. Additive antinociceptive effect of the combination of diazoxide, an activator of ATP-sensitive K+ channels, and sodium nitroprusside and dibutyryl-cGMP. *European Journal of Pharmacology,* 489**,** 59-65.

Ambigapathy, S. 2010. Prevalence of patients with chronic pain and its associated factors in primary care attenders. *Dissertation. Universiti of Malaya*.

Amir, R., Michaelis, M. & Devor, M. 1999. Membrane potential oscillations in dorsal root ganglion neurons: role in normal electrogenesis and neuropathic pain. *Journal of Neuroscience,* 19**,** 8589-8596.

Apkarian, A. V., Sosa, Y., Sonty, S., Levy, R. M., Harden, R. N., Parrish, T. B. & Gitelman, D. R. 2004. Chronic back pain is associated with decreased prefrontal and thalamic gray matter density. *Journal of Neuroscience,* 24**,** 10410-10405.

Arambewela, L. S. R., Arawwawala, M., Owen, N. L. & Jarvis, B. 2007. Volatile Oil of Alpinia galanga Willd. of Sri Lanka. *Journal of Essential Oil Research,* 19**,** 455-456.

Argoff, C. E. & Silvershein, D. I. 2009. A Comparison of Long- and Short-Acting Opioids for the Treatment of Chronic Noncancer Pain: Tailoring Therapy to Meet Patient Needs. *Mayo Clinic Proceedings,* 84**,** 602-612.

Arner, S. & Meyerson, B. A. 1988. Lack of analgesic effect of opioids on neuropathic and idiopathic forms of pain. *Pain,* 33**,** 11-23.

Arroyo, E. J. & Scherer, S. S. 2000. On the molecular architecture of myelinated fibers. *Histochemistry and Cell Biology,* 113**,** 1-18.

Arruda, J. L., Colburn, R. W., Rickman, A. J., Rutkowski, M. D. & Deleo, J. A. 1998. Increase of interleukin-6 mRNA in the spinal cord following peripheral nerve injury in the rat: potential role of IL-6 in neuropathic pain. *Brain Research. Molecular Brain Research,* 62**,** 228-235.

Attal, N., Cruccu, G., Haanpaa, M., Hansson, P., Jensen, T. S., Nurmikko, T., Sampaio, C., Sindrup, S. & Wiffen, P. 2006. EFNS guidelines on pharmacological treatment of neuropathic pain. *European Journal of Neurology,* 13**,** 1153-1169.

Austin, P. J. & Moalem-Taylor, G. 2010. The neuro-immune balance in neuropathic pain: involvement of inflammatory immune cells, immune-like glial cells and cytokines. *Journal of Neuroimmunology,* 229**,** 26-50.

Austin, P. J., Wu, A. & Moalem-Taylor, G. 2012. Chronic Constriction of the Sciatic Nerve and Pain Hypersensitivity Testing in Rats. *Journal of Visualized Experiments : JoVE***,** 3393.

Baby, S., Dan, M., Thaha, A. R. M., Johnson, A. J., Kurup, R., Balakrishnapillai, P. & Lim, C. K. 2009. High content of zerumbone in volatile oils of Zingiber zerumbet from southern India and Malaysia. *Flavour and Fragrance Journal,* 24**,** 301-308.

Backonja, M.-M. 1996. Primary somatosensory cortex and pain perception: Yes sir, your pain is in your head (Part I). *Pain Forum,* 5**,** 174-180.

Bailey, C. P., Couch, D., Johnson, E., Griffiths, K., Kelly, E. & Henderson, G. 2003. μ-Opioid receptor desensitization in mature rat neurons: lack of interaction between DAMGO and morphine. *The Journal of Neuroscience,* 23**,** 10515-10520.

Baliki, M. N., Geha, P. Y., Apkarian, A. V. & Chialvo, D. R. 2008. Beyond feeling: chronic pain hurts the brain, disrupting the default-mode network dynamics. *Journal of Neuroscience,* 28**,** 1398-1403.

Banik, R. K. & Kabadi, R. A. 2013. A modified Hargreaves method for assessing threshold temperatures for heat nociception. *Journal of Neuroscience Methods,* 219**,** 41-51.

Banks, S. M. & Kerns, R. D. 1996. Explaining high rates of depression in chronic pain: A diathesis-stress framework. *Psychological Bulletin,* 119**,** 95.

Barkus, C., Mchugh, S. B., Sprengel, R., Seeburg, P. H., Rawlins, J. N. & Bannerman, D. M. 2010. Hippocampal NMDA receptors and anxiety: at the interface between cognition and emotion. *European Journal of Pharmacology,* 626**,** 49-56.

Baron, R. 2006. Mechanisms of Disease: neuropathic pain[mdash]a clinical perspective. *Nature Clinical Practice Neurology,* 2**,** 95-106.

Basbaum, A. I., Bautista, D. M., Scherrer, G. & Julius, D. 2009. Cellular and Molecular Mechanisms of Pain. *Cell,* 139**,** 267-284.

Basbaum, A. I. & Fields, H. L. 1978. Endogenous pain control mechanisms: review and hypothesis. *Annals of Neurology,* 4**,** 451-462.

Basbaum, A. I. & Fields, H. L. 1984. Endogenous pain control systems: brainstem spinal pathways and endorphin circuitry. *Annual Review of Neuroscience,* 7**,** 309-338.

Be'eri, H., Reichert, F., Saada, A. & Rotshenker, S. 1998. The cytokine network of Wallerian degeneration: IL-10 and GM-CSF. *European Journal of Neuroscience,* 10**,** 2707-2713.

Bekele, T., Bhokre, A. P. & Tesfaye, A. 2015. Tissue reactivity and suture handling characteristics of "jimat" against silk and chromic gut in cat thigh muscle: A comparative study. *Veterinary World,* 8**,** 958-969.

Benbouzid, M., Pallage, V., Rajalu, M., Waltisperger, E., Doridot, S., Poisbeau, P., Freund-Mercier, M. J. & Barrot, M. 2008. Sciatic nerve cuffing in mice: a model of sustained neuropathic pain. *European Journal of Pain,* 12**,** 591-599.

Bennett, G. J. 1993. An animal model of neuropathic pain: A review. *Muscle & Nerve,* 16**,** 1040-1048.

Bennett, G. J. & Xie, Y. K. 1988. A peripheral mononeuropathy in rat that produces disorders of pain sensation like those seen in man. *Pain,* 33**,** 87-107.

Bennett, R., Y'aeger, M., Trapp, A. & Cambre, R. 1997. Histologic evaluation of the tissue reaction to five suture materials in the body wall of rock doves (Columba livia. *Journal of Avian Medicine and Surgery,* 11**,** 175-182.

Benyamin, R., Trescot, A. M., Datta, S., Buenaventura, R., Adlaka, R., Sehgal, N., Glaser, S. E. & Vallejo, R. 2008. Opioid complications and side effects. *Pain Physician,* 11**,** 105-120.

Berger, A. R., Bradley, W. G., Brannagan, T. H., Busis, N. A., Cros, D. P., Dalakas, M. C., Danon, M. J., Donofrio, P., Engel, W. K., England, J. D., Feldman, E. L., Freeman, R. L., Kinsella, L. J., Lacomis, D., Latov, N., Menkes, D. L., Sander, H. W., Thomas, F. P., Triggs, W. J., Windebank, A. J. & Wolfe, G. I. 2003. Guidelines for the diagnosis and treatment of chronic inflammatory demyelinating polyneuropathy. *Journal of the Peripheral Nervous System,* 8**,** 282-284.

Bernard, J. F. & Bandler, R. 1998. Parallel circuits for emotional coping behaviour: new pieces in the puzzle. *Journal of Comparative Neurology,* 401**,** 429-436.

Bernard, J. F. & Besson, J. M. 1990. The spino(trigemio)pontoamygdaloid pathway: electrophysiological evidence for an involvement in pain processes. *Journal of Neurophysiology,* 63**,** 473-490.

Besson, J. M. & Chaouch, A. 1987. Peripheral and spinal mechanisms of nociception. *Physiological Reviews,* 67**,** 67-186.

Bhuiyan, M. N. I., Chowdhury, J. U. & Begum, J. 2008. Chemical investigation of the leaf and rhizome essential oils of Zingiber zerumbet (L.) Smith from Bangladesh. *Bangladesh Journal of Pharmacology,* 4**,** 9-12.

Blackburn-Munro, G. 2004. Pain-like behaviours in animals–how human are they? *Trends in Pharmacological Sciences,* 25**,** 299-305.

Blunck, R., Cordero-Morales, J. F., Cuello, L. G., Perozo, E. & Bezanilla, F. 2006. Detection of the opening of the bundle crossing in KcsA with fluorescence lifetime spectroscopy reveals the existence of two gates for ion conduction. *Journal Of General Physiology,* 128**,** 569-581.

Bolay, H. & Moskowitz, M. A. 2002. Mechanisms of pain modulation in chronic syndromes. *Neurology,* 59**,** 2-7.

Bonezzi, C., Allegri, M., Demartini, L. & Buonocore, M. 2009. The pharmacological treatment of neuropathic pain. *European Journal of Pain Supplements,* 3**,** 85-88.

Bouhassira, D., Lanteri-Minet, M., Attal, N., Laurent, B. & Touboul, C. 2008. Prevalence of chronic pain with neuropathic characteristics in the general population. *Pain,* 136**,** 380-387.

Boulton, A. J., Vinik, A. I., Arezzo, J. C., Bril, V., Feldman, E. L., Freeman, R., Malik, R. A., Maser, R. E., Sosenko, J. M. & Ziegler, D. 2005. Diabetic neuropathies: a statement by the American Diabetes Association. *Diabetes Care,* 28**,** 956-962.

Bourbia, N. & Pertovaara, A. 2011. Is finding the common biological link(s) between pain and affect an infinity quest? *Scandinavian Journal of Pain,* 2**,** 137-138.

Bradman, M. J. G., Ferrini, F., Salio, C. & Merighi, A. 2015. Practical mechanical threshold estimation in rodents using von Frey hairs/Semmes–Weinstein monofilaments: Towards a rational method. *Journal of Neuroscience Methods,* 255**,** 92-103.

Brown, A. K., Christo, P. J. & Wu, C. L. 2004. Strategies for postoperative pain management. *Best Practice & Research Clinical Anaesthesiology,* 18**,** 703-717.

Bullitt, E. 1989. Induction of c -fos -like protein within the lumbar spinal cord and thalamus of the rat following peripheral stimulation. *Brain Research,* 493**,** 391-397.

Burns, T. M. 2008. Guillain-Barre syndrome. *Seminars in Neurology,* 28**,** 152-167.

Busserolles, J., Tsantoulas, C., Eschalier, A. & Lopez Garcia, J. A. 2016. Potassium channels in neuropathic pain: advances, challenges, and emerging ideas. *Pain,* 157 Suppl 1**,** 7-14.

Butt, M. S. & Sultan, M. T. 2011. Ginger and its health claims: molecular aspects. *Critical Reviews in Food Science and Nutrition,* 51**,** 383-393.

Calejesan, A. A., Kim, S. J. & Zhuo, M. 2000. Descending facilitatory modulation of a behavioral nociceptive response by stimulation in the adult rat anterior cingulate cortex. *European Journal of Pain,* 4**,** 83-96.

Campbell, J. N. & Meyer, R. A. 2006. Mechanisms of neuropathic pain. *Neuron,* 52**,** 77-92.

Campbell, V. C. & Welch, S. P. 2001. The role of minoxidil on endogenous opioid peptides in the spinal cord: a putative co-agonist relationship between K-ATP openers and opioids. *European Journal of Pharmacology,* 417**,** 91-98.

Cao, Y., Dreixler, J. C., Roizen, J. D., Roberts, M. T. & Houamed, K. M. 2001. Modulation of recombinant small-conductance Ca(2+)-activated K(+) channels by the muscle relaxant chlorzoxazone and structurally related compounds. *Journal of Pharmacology and Experimental Therapeutics,* 296**,** 683-689.

Cardosa, M. S., Gurpeet, R. & Tee, H. G. T. 2008. Chronic pain. The Third National Health and Morbidity Survey 2006. *Institute for Pubic Health, Ministry of Health Malaysia***,** p262.

Carterall, W. A. 2008. Molecular Mechanisms of Gating and Drug Block of Sodium Channels. *Sodium Channels and Neuronal Hyperexcitability.* John Wiley & Sons, Ltd.

Casey, K. L., Minoshima, S., Berger, K. L., Koeppe, R. A., Morrow, T. J. & Frey, K. A. 1994. Positron emission tomographic analysis of cerebral structures activated specifically by repetitive noxious heat stimuli. *Journal of Neurophysiology,* 71**,** 802-807.

Chang, K. J. & Cuatrecasas, P. 1979. Multiple opiate receptors. Enkephalins and morphine bind to receptors of different specificity. *Journal of Biological Chemistry,* 254**,** 2610-2618.

Chapman, V., Honoré, P., Buritova, J. & Besson, J. M. 1995. The contribution of NMDA receptor activation to spinal c-Fos expression in a model of inflammatory pain. *British Journal of Pharmacology,* 116**,** 1628-1634.

Chavkin, C. 2011. The Therapeutic Potential of [kappa]-Opioids for Treatment of Pain and Addiction. *Neuropsychopharmacology,* 36**,** 369-370.

Chen, B. Y., Lin, D. P., Su, K. C., Chen, Y. L., Wu, C. Y., Teng, M. C., Tsai, Y. T., Sun, C. Y., Wang, S. R. & Chang, H. H. 2011a. Dietary zerumbone prevents against ultraviolet B-induced cataractogenesis in the mouse. *dMolecular Vision,* 17**,** 723-730.

Chen, B. Y., Lin, D. P., Wu, C. Y., Teng, M. C., Sun, C. Y., Tsai, Y. T., Su, K. C., Wang, S. R. & Chang, H. H. 2011b. Dietary zerumbone prevents mouse cornea from UVB-induced photokeratitis through inhibition of NF-kappaB, iNOS, and TNF-alpha expression and reduction of MDA accumulation. *Molecular Vision,* 17**,** 854-863.

Chen, H., Lamer, T. J., Rho, R. H., Marshall, K. A., Sitzman, B. T., Ghazi, S. M. & Brewer, R. P. 2004. Contemporary management of neuropathic pain for the primary care physician. *Mayo Clinic Proceedings,* 79**,** 1533-1545.

Chen, L., Chen, W., Qian, X., Fang, Y. & Zhu, N. 2014. Liquiritigenin alleviates mechanical and cold hyperalgesia in a rat neuropathic pain model. *Scientific Reports,* 4**,** 1-4.

Chen, S.-R., Cai, Y.-Q. & Pan, H.-L. 2009. Plasticity and emerging role of BKCa channels in nociceptive control in neuropathic pain. *Journal of Neurochemistry,* 110**,** 352-362.

Cheng, J. K. & Chiou, L. C. 2006. Mechanisms of the antinociceptive action of gabapentin. *Journal of Pharmacological Sciences,* 100**,** 471-486.

Chi, S. I., Levine, J. D. & Basbaum, A. I. 1993. Peripheral and central contributions to the persistent expression of spinal cord fos-like immunoreactivity produced by sciatic nerve transection in the rat. *Brain Research.,* 617**,** 225-237.

Chia, J. S. M., Omar Farouk, A. A., Mohamad, A. S., Sulaiman, M. R. & Perimal, E. K. 2016. Zerumbone alleviates chronic constriction injury-induced allodynia and hyperalgesia through serotonin 5-HT receptors. *Biomedicine & Pharmacotherapy,* 83**,** 1303-1310.

Chien, T. Y., Huang, S. K. H., Lee, C. J., Tsai, P. W. & Wang, C. C. 2016. Antinociceptive and Anti-Inflammatory Effects of Zerumbone against Mono-Iodoacetate-Induced Arthritis. *International Journal of Molecular Sciences,* 17**,** 249.

Chiu, I. M., Von Hehn, C. A. & Woolf, C. J. 2012. Neurogenic Inflammation – The Peripheral Nervous System's Role in Host Defense and Immunopathology. *Nature Neuroscience,* 15**,** 1063-1067.

Chong, M. S. & Bajwa, Z. H. 2003. Diagnosis and Treatment of neuropathic pain. *Journal of Pain and Symptom Management,* 25**,** 4-11.

Christensen, M. D., Everhart, A. W., Pickelman, J. T. & Hulsebosch, C. E. 1996. Mechanical and thermal allodynia in chronic central pain following spinal cord injury. *Pain,* 68**,** 97-107.

Chung, K., Lee, B. H., Yoon, Y. W. & Chung, J. M. 1996. Sympathetic sprouting in the dorsal root ganglia of the injured peripheral nerve in a rat neuropathic pain model. *Journal of Comparative Neurology,* 376**,** 241-252.

Clatworthy, A. L., Illich, P. A., Castro, G. A. & Walters, E. T. 1995. Role of peri-axonal inflammation in the development of thermal hyperalgesia and guarding behaviour in a rat model of neuropathic pain. *Neuroscience Letters,* 184**,** 5-8.

Coggeshall, R. E. 2005. Fos, nociception and the dorsal horn. *Progress in Neurobiology,* 77**,** 299-352.

Coleman, M. P. & Freeman, M. R. 2010. Wallerian degeneration.Wld(S), and Nmnat. *Annual Review in Neuroscience.,* 1802**,** 245-267.

Colleoni, M. & Sacedote, P. 2010. Murine models of human neuropathic pain. *Biochimica et Biophysica Acta,* 1802**,** 924-933.

Costa, B., Comelli, F., Bettoni, I., Colleoni, M. & Giagnoni, G. 2008. The endogenous fatty acid amide, palmitoylethanolamide, has anti-allodynic and anti-hyperalgesic effects in a murine model of neuropathic pain: involvement of CB1, TRPV1 and PPARγ receptors and neurotrophic factors. *Pain,* 139**,** 541-550.

Costigan, M., A., M., Latremoliere, A., Johnston, C., Verma-Gandhu, M., Herbert, T. A., Barrett, L., Brenner, G. J., Vardeh, D., Woolf, C. J. & Fitzgerald, M. 2009. T-cell infiltration and signaling in the adult dorsal spinal cord is a major contributor to neuropathic pain-like hypersensitivity. *Journal of Neuroscience,* 29**,** 14415-14422.

Cox, J. J., Reimann, F., Nicholas, A. K., Thornton, G., Roberts, E., Springell, K., Karbani, G., Jafri, H., Mannan, J., Raashid, Y., Al-Gazali, L., Hamamy, H., Valente, E. M., Gorman, S., Williams, R., Mchale, D. P., Wood, J. N., Gribble, F. M. & Woods, C. G. 2006. An SCN9A channelopathy causes congenital inability to experience pain. *Nature,* 444**,** 894-898.

Cragg, G. M. & Newman, D. J. 2005. Biodiversity: A continuing source of novel drug leads. *Pure and Applied Chemistry,* 77**,** 7-24.

Craig, W. J. 1999. Health-promoting properties of common herbs. *The American Journal of Clinical Nutrition,* 70**,** 491-499.

Craven, J. 2008. Major ascending and descending tracts in the spinal cord. *Anaesthesia & Intensive Care Medicine,* 9**,** 1-2.

Crofford, L. J. 2013. Use of NSAIDs in treating patients with arthritis. *Arthritis Research & Therapy,* 15**,** 2.

Cui, J., Yang, H. & Lee, U. S. 2009. Molecular mechanisms of BK channel activation. *Cellular and Molecular Life Sciences,* 66**,** 852-875.

Cummins, T. R. 2007. Setting up for the block: the mechanism underlying lidocaine's use-dependent inhibition of sodium channels. *The Journal of Physiology,* 582**,** 11.

Cummins, T. R., Rush, A. M., Estacion, M., Dib-Hajj, S. D. & Waxman, S. G. 2009. Voltage-clamp and current-clamp recordings from mammalian DRG neurons. *Nature Protocols,* 4**,** 1103-1112.

Curran, T., Bravo, R. & Muller, R. 1985. Transient induction of c-fos and c-myc in an immediate consequence of growth factor stimulation. *Cancer Survival,* 4**,** 655-681.

Curran, T. & Teich, N. M. 1982. Identification of a 39,000-dalton protein in cells transformed by the FBJ murine osteosarcoma virus. *Virology,* 116**,** 221-235.

Curran, T. & Verma, I. M. 1984. FBR murine osteosarcoma virus. I. Molecular analysis and characterization of a 75,000-Da gag-fos fusion product. *Virology,* 135**,** 218-228.

Daniell, H. W. 2002. Hypogonadism in men consuming sustained-action oral opioids. *Journal of Pain,* 3**,** 377-384.

Daniell, H. W. 2008. Opioid endocrinopathy in women consuming prescribed sustained-action opioids for control of nonmalignant pain. *Journal of Pain,* 9**,** 28-36.

Davis, K. D., Taylor, S. J., Crawley, A. P., Wood, M. L. & Mikulis, D. J. 1997. Functional MRI of pain- and attention-related activations in the human cingulate cortex. *Journal of Neurophysiology,* 77**,** 3370-33780.

Davis, M. P. & Walsh, D. 2004. Epidemiology of cancer pain and factors influencing poor pain control. . *American Journal of Hospice & Palliative Care,* 21**,** 137-142.

De Vry, J., Kuhl, E., Franken-Kunkel, P. & Eckel, G. 2004. Pharmacological characterization of the chronic constriction injury model of neuropathic pain. *Eur J Pharmacol,* 491**,** 137-148.

Decosterd, I. & Woolf, C. J. 2000. Spared nerve injury: an animal model of persistent peripheral neuropathic pain. *Pain,* 87**,** 149-158.

Del Camino, D., Holmgren, M., Liu, Y. & Yellen, G. 2000. Blocker protection in the pore of a voltage-gated K+ channel and its structural implications. *Nature,* 403**,** 321-325.

Del Rey, A., Yau, H. J., Randolf, A., Centeno, M. V., Wildmann, J., Martina, M., Besedovsky, H. O. & Apkarian, A. V. 2011. Chronic neuropathic pain-like behavior correlates with IL-1beta expression and disrupts cytokine interactions in the hippocampus. *Pain,* 152**,** 2827-2835.

Deleo, J. A., Colburn, R. W., Nichols, M. & Malhotra, A. 1996. Interleukin-6-mediated hyperalgesia/allodynia and increased spinal IL-6 expression in a rat mononeuropathy model. *Journal of Interferon & Cytokine Research,* 16**,** 695-700.

Deleo, J. A., Coombs, D. W., Willenbring, S., Colburn, R. W., Fromm, C., Wagner, R. & Twitchell, B. B. 1994. Characterization of a neuropathic pain model: sciatic cryoneurolysis in the rat. *Pain,* 56**,** 9-16.

Dev, S. 1960. Studies in sesquiterpenes—XVI. *Tetrahedron,* 8**,** 171-180.

Devor, M., Janig, W. & Michaelis, M. 1994. Modulation of activity in dorsal root ganglion neurons by sympathetic activation in nerve-injured rats. *Journal of Neurophysiology,* 71**,** 38-47.

Djouhri, L., Koutsikou, S., Fang, X., Mcmullan, S. & Lawson, S. N. 2006. Spontaneous pain, both neuropathic and inflammatory, is related to frequency of spontaneous firing in intact C-fiber nociceptors. *Journal of Neuroscience,* 26**,** 1281-1292.

Djouhri, L. & Lawson, S. N. 2004. Abeta-fiber nociceptive primary afferent neurons: a review of incidence and properties in relation to other afferent A-fiber neurons in mammals. *Brain Research Reviews,* 46**,** 131-145.

Dominguez, E., Mauborgne, A., Mallet, J., Desclaux, M. & Pohl, M. 2010. SOCS3-mediated blockade of JAK/STAT3 signaling pathway reveals its major contribution to spinal cord neuroinflammation and mechanical allodynia after peripheral nerve injury. *Journal of Neuroscience,* 30**,** 5754-5766.

Dougherty, P. M., Cata, J. P., Cordella, J. V., Burton, A. & Weng, H.-R. 2004. Taxol-induced sensory disturbance is characterized by preferential impairment of myelinated fiber function in cancer patients. *Pain,* 109**,** 132-142.

Dowdall, T., Robinson, I. & Meert, T. F. 2005. Comparison of five different rat models of peripheral nerve injury. *Pharmacology Biochemistry and Behavior,* 80**,** 93-108.

Drake, C. T., Chavkin, C. & Milner, T. A. 2007. Opioid systems in the dentate gyrus. *Progress in Brain Research,* 163**,** 245-263.

Dubin, A. E. & Patapoutian, A. 2010. Nociceptors: the sensors of the pain pathway. *The Journal of Clinical Investigation,* 120**,** 3760-3772.

Dubovy, P., Jancalek, R., Klusakova, I., Svizenska, I. & Pejchalova, K. 2006. Intra- and extraneuronal changes of immunofluorescence staining for TNF-alpha and TNFR1 in the dorsal root ganglia of rat peripheral neuropathic pain models. *Cellular and Molecular Neurobiology,* 26**,** 1205-1217.

Dumas, E. O. & Pollack, G. M. 2008. Opioid Tolerance Development: A Pharmacokinetic/Pharmacodynamic Perspective. *American Association of Pharmaceutical Scientists,* 10**,** 537.

Dunn, D. 2007. Wound Closure Manual. USA: Ethicon: A Johnson and Johnson Company. *USA: Ethicon: A Johnson and Johnson Company***,** pp. 9–40.

Duric, V. & Mccarson, K. E. 2005. Hippocampal neurokinin-1 receptor and brain-derived neurotrophic factor gene expression is decreased in rat models of pain and stress. *Neuroscience Letters,* 133**,** 999-1006.

Dworkin, R. H., Backonja, M., Rowbotham, M. C., Allen, R. R., Argoff, C. R., Bennett, G. J., Bushnell, M. C., Farrar, J. T., Galer, B. S. & Haythornthwaite, J. A. 2003. Advances in neuropathic pain: diagnosis, mechanisms, and treatment recommendations. *Archives of Neurology,* 60**,** 1524-1534.

Dworkin, R. H., O'connor, A. B., Audette, J., Baron, R., Gourlay, G. K., Haanpää, M. L., Kent, J. L., Krane, E. J., Lebel, A. A., Levy, R. M., Mackey, S. C., Mayer, J., Miaskowski, C., Raja, S. N., Rice, A. S. C., Schmader, K. E., Stacey, B., Stanos, S., Treede, R.-D., Turk, D. C., Walco, G. A. & Wells, C. D. 2010. Recommendations for the Pharmacological Management of Neuropathic Pain: An Overview and Literature Update. *Mayo Clinic Proceedings,* 85**,** 3-14.

Eguchi, A., Kaneko, Y., Murakami, A. & Ohigashi, H. 2007. Zerumbone suppresses phorbol ester-induced expression of multiple scavenger receptor genes in THP-1 human monocytic cells. *Bioscience, Biotechnology, and Biochemistry,* 71**,** 935–945.

Eisenberg, E., Mcnicol, E. D. & Carr, D. B. 2005. Efficacy and safety of opioid agonists in the treatment of neuropathic pain of nonmalignant origin: systematic review and meta-analysis of randomized controlled trials. *Jama,* 293**,** 3043-3052.

Elliott, K. J., Brodsky, M., Hynansky, A. D., Foley, K. M. & Inturrisi, C. E. 1995. Dextromethorphan suppresses both formalin-induced nociceptive behavior and the formalin-induced increase in spinal cord c-fos mRNA. *Pain,* 61**,** 401-409.

Faber, E. S. & Sah, P. 2003. Calcium-activated potassium channels: multiple contributions to neuronal function. *Neuroscientist,* 9**,** 181-194.

Faber, E. S. L. & Sah, P. 2007. FUNCTIONS OF SK CHANNELS IN CENTRAL NEURONS. *Clinical and Experimental Pharmacology and Physiology,* 34**,** 1077-1083.

Finn, A. K. & Whistler, J. L. 2001. Endocytosis of the mu opioid receptor reduces tolerance and a cellular hallmark of opiate withdrawal. *Neuron,* 32**,** 829-839.

Flor, H., Nikolajsen, L. & Staehelin Jensen, T. 2006. Phantom limb pain: a case of maladaptive CNS plasticity? *Nature Reviews Neuroscience,* 7**,** 873-881.

Fossum, T., Hedlund, C. S. & Johnson, A. L. 1997. Small Animal Surgery. *2nd ed. St. Louis, USA: Mosby***,** 42.

Fregnan, F., Muratori, L., Simões, A. R., Giacobini-Robecchi, M. G. & Raimondo, S. 2012. Role of inflammatory cytokines in peripheral nerve injury. *Neural Regeneration Research,* 7**,** 2259-2266.

Furukawa, N., Takasusuki, T., Fukushima, T. & Hori, Y. 2008. Presynaptic large-conductance calcium-activated potassium channels control synaptic transmission in the superficial dorsal horn of the mouse. *Neuroscience Letters,* 444**,** 79-82.

Ganabadi, S. & Kadir, S. F. A. 2009. Zerumbone's Effect on Major Histocompatibility Complex Type II Cells in Synovial Membrane of OsteoArthritic Joint. *Research Journal of Veterinary Sciences,* 2**,** 14-20.

Gao, Y. J. & Ji, R. R. 2009. c-Fos or pERK, Which is a Better Marker for Neuronal Activation and Central Sensitization After Noxious Stimulation and Tissue Injury? *The Open Pain Journal,* 2**,** 11-17.

Gaudet, A. D., Popovich, P. G. & Ramer, M. S. 2011. Wallerian degeneration: Gaining perspective on inflammatory events after peripheral nerve injury. *Journal of Neuroinflammation,* 8**,** 110.

Gaveriaux-Ruff, C., Karchewski, L. A., Hever, X., Matifas, A. & Kieffer, B. L. 2008. Inflammatory pain is enhanced in delta opioid receptor-knockout mice. *European Journal of Neuroscience,* 27**,** 2558-2567.

Genevay, S., Stingelin, S. & Gabay, C. 2004. Efficacy of etanercept in the treatment of acute, severe sciatica: a pilot study. *Annals of the Rheumatic Diseases,* 63**,** 1120-1123.

Genovese, T., Esposito, E., Mazzon, E., Di Paola, R., Caminiti, R., Bramanti, P., Cappelani, A. & Cuzzocrea, S. 2009. Absence of endogenous interleukin-10 enhances secondary inflammatory process after spinal cord compression injury in mice. *Journal of Neurochemistry,* 108**,** 1360-1372.

George, A., Kleinschnitz, C., Zelenka, M., Brinkhoff, J., Stoll, G. & Sommer, C. 2004. Wallerian degeneration after crush or chronic constriction injury of rodent sciatic nerve is associated with a depletion of endoneurial interleukin-10 protein. *Experimental Neurology,* 188**,** 187-191.

Geuna, S., Raimondo, S., Ronchi, G., Di Scipio, F., Tos, P., Czaja, K. & Fornaro, M. 2009. Chapter 3: Histology of the peripheral nerve and changes occurring during nerve regeneration. *International Review of Neurobiologyl,* 87**,** 27-46.

Gomar, A., Hosseini, A. & Mirazi, N. 2014. Memory enhancement by administration of ginger (Zingiber officinale)

extract on morphine-induced memory impairment in male rats. *Journal of Acute Disease,* 2014**,** 212-217.

Goodman, A. J., Le Bourdonnec, B. & Dolle, R. E. 2007. Mu opioid receptor antagonists: recent developments. *ChemMedChem,* 2**,** 1552-1570.

Gore, M., Brandenburg, N. A., Dukes, E., Hoffman, D. L., Tai, K. S. & Stacey, B. 2005. Pain severity in diabetic peripheral neuropathy is associated with patient functioning, symptom levels of anxiety and depression, and sleep. *Journal of Pain and Symptom Management,* 30**,** 374-385.

Grace, P. M., Hutchinson, M. R., Manavis, J., Somogyi, A. A. & Rolan, P. E. 2010. A novel animal model of graded neuropathic pain: Utility to investigate mechanisms of population heterogeneity. *Journal of Neuroscience Methods,* 193**,** 47-53.

Granados-Soto, V., Argüelles, C. F. & Ortiz, M. I. 2002. The peripheral antinociceptive effect of resveratrol is associated with activation of potassium channels. *Neuropharmacology,* 43**,** 917-923.

Gribble, F. M. & Reimann, F. 2003. Sulphonylurea action revisited: the post-cloning era. *Diabetologia,* 46**,** 875-891.

Grizel, A. V., Glukhov, G. S. & Sokolova, O. S. 2014. Mechanisms of Activation of Voltage-Gated Potassium Channels. *Acta Naturae,* 6**,** 10-26.

Guneli, E., Onal, A., Ates, M., Bagriyanik, H. A., Resmi, H., Orhan, C. E., Kolatan, H. E. & Gumustekin, M. 2010. Effects of of repeated administered ghrelin on chronic constriction injury of the sciatic nerve in rats. *Neuroscience Letters,* 479**,** 226-230.

Gutman, G. A., Chandy, K. G., Adelman, J. P., Aiyar, J., Bayliss, D. A., Clapham, D. E., Covarriubias, M., Desir, G. V., Furuichi, K., Ganetzky, B., Garcia, M. L., Grissmer, S., Jan, L. Y., Karschin, A., Kim, D., Kuperschmidt, S., Kurachi, Y., Lazdunski, M., Lesage, F., Lester, H. A., Mckinnon, D., Nichols, C. G., O'kelly, I., Robbins, J., Robertson, G. A., Rudy, B., Sanguinetti, M., Seino, S., Stuehmer, W., Tamkun, M. M., Vandenberg, C. A., Wei, A., Wulff, H. & Wymore, R. S. 2003. International Union of Pharmacology. XLI. Compendium of Voltage-Gated Ion Channels: Potassium Channels. *Pharmacological Reviews,* 55**,** 583-586.

Gutman, G. A., Chandy, K. G., Grissmer, S., Lazdunski, M., Mckinnon, D., Pardo, L. A., Robertson, G. A., Rudy, B., Sanguinetti, M. C., Stuhmer, W. & Wang, X. 2005. International Union of Pharmacology. LIII. Nomenclature and molecular relationships of voltage-gated potassium channels. *Pharmacological Reviews,* 57**,** 473-508.

Gwynn, J. 2015. Pregabalin is only partially effective for neuropathic pain. *Bmj,* 350**,** h3478.

Habsah, M., Amran, M., Mackeen, M. M., Lajis, N. H., Kikuzaki, H., Nakatani, N., Rahman, A. A., Ghafar. & Ali, A. M. 2000. Screening of Zingiberaceae extracts for antimicrobial and antioxidant activities. *Journal of Ethnopharmacology,* 72**,** 403-410.

Han, J. S. & Neugebauer, V. 2004. Synaptic plasticity in the amygdala in a visceral pain model in rats. *Neuroscience Letters,* 361**,** 254-257.

Hargreaves, K., Dubner, R., Brown, F., Flores, C. & Joris, J. 1988. A new and sensitive method for measuring thermal nociception in cutaneous hyperalgesia. *Pain.,* 32.

Harris, J. A. 1998. Using c-fos as a neural marker of pain. *Brain Research Bulletin,* 45**,** 1-8.

Herdegen, T., Kovary, K., Leah, J. & Bravo, R. 1991. Specific temporal and spatial distribution of JUN, FOS, and KROX-24 proteins in spinal neurons following noxious transsynaptic stimulation. *Journal of Comparative Neurology,* 313**,** 178-191.

Hill, M. A., Yang, Y., Ella, S. R., Davis, M. J. & Braun, A. P. 2010. Large Conductance, Ca(2+)-Activated K(+) Channels (BK(Ca)) and Arteriolar Myogenic Signaling. *FEBS letters,* 584**,** 2033-2042.

Hochberg, J., Meyer, K. M. & Marion, M. D. 2009. Suture choice and other methods of skin closure. *Surgical Clinics of North America,* 89**,** 627-641.

Hojsted, J. & Sjogren, P. 2007. An update on the role of opioids in the management of chronic pain of nonmalignant origin. *Current Opinion in Anesthesiology,* 20**,** 451-455.

Honoré, P. H., Basnet, A., Kristensen, P., Andersen, L. M., Neustrup, S., Møllgaard, P., Eljaja, L. & Bjerrum, O. J. 2011. Predictive validity of pharmacologic interventions in animal models of neuropathic pain. *Scandinavian Journal of Pain,* 2**,** 178-184.

Horrigan, F. T., Cui, J. & Aldrich, R. W. 1999. Allosteric voltage gating of potassium channels I. Mslo ionic currents in the absence of Ca(2+). *Journal of General Physiology,* 114**,** 277-304.

Hovaguimian, A. & Gibbons, C. H. 2011. Diagnosis and treatment of pain in small-fiber neuropathy. *Current Pain and Headache Reports,* 15**,** 193-200.

Hsu, E. & Cohen, S. P. 2013. Postamputation pain: epidemiology, mechanisms, and treatment. *Journal of Pain Research,* 6**,** 121-136.

Hsu, M. M. & Shyu, B. C. 1997. Electrophysiological study of the connection between medial thalamus and anterior cingulate cortex in the rat. *Neuroreport,* 8**,** 2701-2707.

Hu, P., Bembrick, A. L., Keay, K. A. & Mclachlan, E. M. 2007. Immune cell involvement in dorsal root ganglia and spinal cord after chronic constriction or transection of the rat sciatic nerve. *Brain, Behavior, and Immunity,* 21**,** 599-616.

Hunt, S. P., Pini, A. & Eva, G. 1987. Induction of c-fos-like protein in spinal cord neurons following sensory stimulation. *Nature,* 32**,** 632-634.

Hutchison, W. D., Davis, K. D., Lozano, A. M., Tasker, R. R. & Dostrovsky, J. O. 1999. Pain-related neurons in the human cingulate cortex. *Nature Neuroscience,* 2**,** 403-405.

IASP. 2015. Global year against neuropathic pain. Available at: http://www.iasp-pain.org/GlobalYear/NeuropathicPain?navItemNumber=580. Accessed December 19, 2016

IASP. 2012. ISAP taxonomy. Available at: http://www.iasp-pain.org/Education/Content.aspx?ItemNumber=1698&navItemNumber=576. Accessed December 19, 2016

Ikeda, M. & Oka, Y. 2012. The relationship between nerve conduction velocity and fiber morphology during peripheral nerve regeneration. *Brain and Behavior,* 2**,** 382-390.

Ippolito, D. L., Temkin, P. A., Rogalski, S. L. & Chavkin, C. 2002. N-terminal tyrosine residues within the potassium channel Kir3 modulate GTPase activity of Galphai. *Journal of Biological Chemistry,* 277**,** 32692-32696.

ITIS. Retrieved [June, 23, 2016], from the Integrated Taxonomic Information System on-line database, http://www.itis.gov

Iwatsuki, K., Arai, T., Ota, H., Kato, S., Natsume, T., Kurimoto, S., Yamamoto, M. & Hirata, H. 2013. Targeting anti-inflammatory treatment can ameliorate injury-induced neuropathic pain. *PLoS One,* 8**,** e57721.

Jaggi, A. S., Jain, V. & Singh, N. 2011. Animal models of neuropathic pain. *Fundamental & Clinical Pharmacology* 25**,** 1-28.

Jang, D. S. & Seo, E. K. 2005. Potentially bioactive two new natural sesquiterpenoids from the rhizomes of Zingiber zerumbet. *Archives of Pharmacal Research,* 28**,** 294-296.

Jantan, I., Raweh, S. M., Sirat, H. M., Jamil, S., Mohd Yasin, Y. H., Jalil, J. & Jamal, J. A. 2008. Inhibitory effect of compounds from Zingiberaceae species on human platelet aggregation. *Phytomedicine,* 15**,** 306-309.

Jasmin, L., Kohan, L., Franssen, M., Janni, G. & Goff, J. R. 1998. The cold plate as a test of nociceptive behaviors: description and application to the study of chronic neuropathic and inflammatory pain models. *Pain,* 75**,** 367-382.

Jasmin, L., Wang, H., Tarczy-Hornoch, K., Levine, J. & Basbaum, A. 1994. Differential effects of morphine on noxious stimulus-evoked fos-like immunoreactivity in subpopulations of spinoparabrachial neurons. *The Journal of Neuroscience,* 14**,** 7252-7260.

Jensen, T. S., Baron, R., Haanpaa, M., Kalso, E., Loeser, J. D., Rice, A. S. & Treede, R. D. 2011. A new definition of neuropathic pain. *Pain,* 152**,** 2204-2205.

Jensen, T. S. & Finnerup, N. B. 2014. Allodynia and hyperalgesia in neuropathic pain: clinical manifestations and mechanisms. *Lancet Neurology,* 13**,** 924-935.

Jergova, S. & Cizkova, D. 2005. Long-term changes of c-Fos expression in the rat spinal cord following chronic constriction injury. *European Journal of Pharmacology,* 9**,** 345-354.

Ji, R. R., Gereau, R. W., Malcangio, M. & Strichartz, G. R. 2009. MAP kinase and pain. *Brain Research Reviews,* 60**,** 135-148.

Ji, R. R., Kohno, T., Moore, K. A. & Woolf, C. J. 2003. Central sensitization and LTP: do pain and memory share similar mechanisms? *Trends in Neurosciences,* 26**,** 696-705.

Jones, P., Griffin, A. M., Gawell, L., Lavoie, R., Delorme, D., Roberts, E., Brown, W., Walpole, C., Xiao, W., Boulet, J., Labarre, M., Coupal, M., Butterworth, J., St-Onge, S., Hodzic, L. & Salois, D. 2009. N,N-Diethyl-4-[(3-hydroxyphenyl)(piperidin-4-yl)amino] benzamide derivatives: the development of diaryl amino piperidines as potent delta opioid receptor agonists with in vivo anti-nociceptive activity in rodent models. *Bioorganic & Medicinal Chemistry Letters,* 19**,** 5994-5998.

Julius, D. & Basbaum, A. I. 2001. Molecular mechanisms of nociception. *Nature,* 413**,** 203-210.

Kader, G., Nikkon, F., Rashid, M. A. & Yeasmin, T. 2011. Antimicrobial activities of the rhizome extract of Zingiber zerumbet Linn. *Asian Pacific Journal of Tropical Biomedicine,* 1**,** 409-412.

Kajander, K. C., Pollock, C. H. & Berg, H. 1996. Evaluation of hindpaw position in rats during chronic constriction injury (CCI) produced with different suture materials. *Somatosensory & Motor Research,* 13**,** 95-101.

Kapitzke, D., Vetter, I. & Cabot, P. J. 2005. Endogenous opioid analgesia in peripheral tissues and the clinical implications for pain control. *Therapeutics and Clinical Risk Management,* 1**,** 279-297.

Kapoor, S. 2012. The rapidly emerging role of zerumbone in attenuating tumor growth in systemic malignancies. *Molecular Nutrition & Food Research,* 56**,** 1487.

Kauppila, T. 1998. Correlation between autotomy-behavior and current theories of neuropathic pain. *Neuroscience & Biobehavioral Reviews,* 23**,** 111-129.

Kawahara, K., Hohjoh, H., Inazumi, T., Tsuchiya, S. & Sugimoto, Y. 2015. Prostaglandin E2-induced inflammation: Relevance of prostaglandin E receptors. *Biochimica et Biophysica Acta,* 1851**,** 414-421.

Kawano, T., Zoga, V., Gemes, G., Mccallum, J. B., Wu, H. E., Pravdic, D., Liang, M. Y., Kwok, W. M., Hogan, Q. & Sarantopoulos, C. 2009. Suppressed Ca2+/CaM/CaMKII-dependent K(ATP) channel activity in primary afferent neurons mediates hyperalgesia after axotomy. *Proceedings of the National Academy of Sciences of the United States of America,* 106**,** 8725-8730.

Kehlet, H., Jensen, T. S. & Woolf, C. J. 2006. Persistent postsurgical pain: risk factors and prevention. *Lancet,* 367**,** 1618-1625.

Kennedy, J. D. 2007. Neuropathic pain: molecular complexity underlies continuing unmet medical need. *Journal of Medicinal Chemistry,* 50**,** 2547-2556.

Kim, D. S., Choi, J. O., Rim, H. D. & Cho, H. J. 2002. Downregulation of voltage-gated potassium channel alpha gene expression in dorsal root ganglia following chronic constriction injury of the rat sciatic nerve. *Brain Research. Molecular Brain Research,* 105**,** 146-152.

Kim, H. K., Kim, J. H., Gao, X., Zhou, J. L., Lee, I., Chung, K. & Chung, J. M. 2006. Analgesic effect of vitamin E is mediated by reducing central sensitization in neuropathic pain. *Pain,* 122**,** 53-62.

Kim, H. K., Park, S. K., Zhou, J. L., Taglialatela, G., Chung, K., Coggeshall, R. E. & Chung, J. M. 2004. Reactive oxygen species (ROS) play an important role in a rat model of neuropathic pain. *Pain,* 111**,** 116-124.

Kim, K. J., Yoon, Y. W. & Chung, J. M. 1997. Comparison of three rodent neuropathic pain models. *Experimental Brain Research,* 113**,** 200-206.

Kim, M., Miyamoto, S., Yasui, Y., Oyama, T., Murakami, A. & Tanaka, T. 2009. Zerumbone, a tropical ginger sesquiterpene, inhibits colon and lung carcinogenesis in mice. *International Journal of Cancer,* 124**,** 264-271.

Kim, S. H. & Chung, J. M. 1992. An experimental model for peripheral neuropathy produced by segmental spinal nerve ligation in the rat. *Pain,* 50**,** 355-363.

Kishore, N. & Dwivedi, R. S. 1992. Zerumbone: a potential fungitoxic agent isolated from Zingiber cassumunar Roxb. *Mycopathologia,* 120**,** 155-159.

Kleinschnitz, C., Hofstetter, H. H., Meuth, S. G., Braeuninger, S., Sommer, C. & Stoll, G. 2006. T cell infiltration after chronic constriction injury of mouse sciatic nerve is associated with interleukin-17 expression. *Experimental Neurology,* 200**,** 480-485.

Koch, T. & Höllt, V. 2008. Role of receptor internalization in opioid tolerance and dependence. *Pharmacology & Therapeutics,* 117**,** 199-206.

Kodama, D., Ono, H. & Tanabe, M. 2007a. Altered hippocampal long-term potentiation after peripheral nerve injury in mice. *European Journal of Pharmacology,* 574**,** 127-132.

Kodama, D., Ono, H. & Tanabe, M. 2007b. Altered hippocampal long-term potentiation after peripheral nerve injury in mice. *Journal of Pharmacology,* 574**,** 127-132.

Kodama, D., Ono, H. & Tanabe, M. 2011. Increased hippocampal glycine uptake and cognitive dysfunction after peripheral nerve injury. *Pain,* 152**,** 809-817.

Koltzenburg, M., Lundberg, L. E. & Torebjork, H. E. 1992. Dynamic and static components of mechanical hyperalgesia in human hairy skin. *Pain,* 51**,** 207-219.

Korhonen, T., Karppinen, J., Paimela, L., Malmivaara, A., Lindgren, K. A., Bowman, C., Hammond, A., Kirkham, B., Jarvinen, S., Niinimaki, J., Veeger, N., Haapea, M., Torkki, M., Tervonen, O., Seitsalo, S. & Hurri, H. 2006. The treatment of disc-herniation-induced sciatica with infliximab: one-year follow-up results of FIRST II, a randomized controlled trial. *Spine (Phila Pa 1976),* 31**,** 2759-2766.

Kosten, T. R. & George, T. P. 2002. The Neurobiology of Opioid Dependence: Implications for Treatment. *Science & Practice Perspectives,* 1**,** 13-20.

Krugers, H. J., Lucassen, P. J., Henk Karst, H. & Joëls, M. 2010. Chronic stress effects on hippocampal structure and synaptic function: relevance for depression and normalization by anti‐glucocorticoid treatment. *Frontiers in Synaptic Neuroscience,* 2**,** 1-10.

Lacomis, D. & Zivkovic, S. A. 2007. Approach to vasculitic neuropathies. *Journal of Clinical Neuromuscular Disease,* 9**,** 265-276.

Langner, E., Greifenberg, S. & Gruenwald, J. 1997. Ginger: history and use. *Advances in therapy,* 15**,** 25-44.

Latremoliere, A. & Woolf, C. J. 2009. Central sensitization: a generator of pain hypersensitivity by central neural plasticity. *Journal of Pain,* 10**,** 895-926.

Lavich, T. R., Cordeiro, R. S. B., Silva, P. M. R. & Martins, M. A. 2005. A novel hot-plate test sensitive to hyperalgesic stimuli and non-opioid analgesics. *Brazilian Journal of Medical and Biological Research,* 38**,** 445-451.

Le Bourdonnec, B., Windh, R. T., Ajello, C. W., Leister, L. K., Gu, M., Chu, G. H., Tuthill, P. A., Barker, W. M., Koblish, M., Wiant, D. D., Graczyk, T. M., Belanger, S., Cassel, J. A., Feschenko, M. S., Brogdon, B. L., Smith, S. A., Christ, D. D., Derelanko, M. J., Kutz, S., Little, P. J., Dehaven, R. N., Dehaven-Hudkins, D. L. & Dolle, R. E. 2008. Potent, orally bioavailable delta opioid receptor agonists for the treatment of pain: discovery of N,N-diethyl-4-(5-hydroxyspiro[chromene-2,4'-piperidine]-4-yl)benzamide (ADL5859). *Journal of Medicinal Chemistry,* 51**,** 5893-5896.

Lee, B. H., Won, R., Baik, E. J., Lee, S. H. & Moon, C. H. 2000. An animal model of neuropathic pain employing injury to the sciatic nerve branches. *Neuroreport,* 11**,** 657-661.

Lees, J. G., Duffy, S. S. & Moalem-Taylor, G. 2013. Immunotherapy targeting cytokines in neuropathic pain. *Frontiers in Pharmacology,* 4**,** 142.

Lei, L. G., Sun, S., Gao, Y. J., Zhao, Z. Q. & Zhang, Y. Q. 2004. NMDA receptors in the anterior cingulate cortex mediate pain-related aversion. *Experimental Neurology,* 189**,** 413-421.

Leita-Almeida, H., Guimarães, M. R., Cerqueira, J. J., Ribeiro-Costa, N., Martins, H. A., Sousa, N. & Almeida, A. 2014. Asymmetric c-fos expression in the ventral orbital cortex is associated with impaired reversal learning in a right-sided neuropathy. *Molecular Pain,* 10**,** 41.

Lewin, G. R. & Moshourab, R. 2004. Mechanosensation and pain. *J Neurobiol,* 61**,** 30-44.

Li, W., Ailin, L., Honghui, Y. & Yuke, T. 2005. Effect of touch-stimulus on the expression of C-fos and TrkA in spinal cord following chronic constriction injury of the sciatic nerve in rats. *Journal of Huazhong University of Science and Technology [Medical Sciences],* 25**,** 219-222.

Li, X. Y., Ko, H. G., Chen, T., Descalzi, G., Koga, K., Wang, H., Kim, S. S., Shang, Y., Kwak, C., Park, S. W., Shim, J., Lee, K., Collingridge, G. L., Kaang, B. K. & Zhuo, M. 2010. Alleviating neuropathic pain hypersensitivity by inhibiting PKMzeta in the anterior cingulate cortex. *Science,* 330**,** 1400-1404.

Liang, C., Tao, Y., Shen, C., Tan, Z., Xiong, W., C. & Mei, L. 2012. Erbin Is Required for Myelination in Regenerated Axonsafter Injury. *The Journal of Neuroscience,* 32**,** 15169-15180.

Lindenlaub, T., Teuteberg, P., Hartung, T. & Sommer, C. 2000. Effects of neutralizing antibodies to TNF-alpha on pain-related behavior and nerve regeneration in mice with chronic constriction injury. *Brain Research,* 866**,** 15-22.

Liu, B., Linley, J. E., Du, X., Zhang, X., Ooi, L., Zhang, H. & Gamper, N. 2010. The acute nociceptive signals induced by bradykinin in rat sensory neurons are mediated by inhibition of M-type K+ channels and activation of Ca2+-activated Cl- channels. *Journal of Clinical Investigation,* 120**,** 1240-1252.

Liu, C.-Y., Lu, Z.-Y., Li, N., Yu, L.-H., Zhao, Y.-F. & Ma, B. 2015. The role of large-conductance, calcium-activated potassium channels in a rat model of trigeminal neuropathic pain. *Cephalalgia,* 35**,** 16-35.

Liu, M. & Wood, J. N. 2011. The Roles of Sodium Channels in Nociception: Implications for Mechanisms of Neuropathic Pain. *Pain Medicine,* 12**,** S93-S99.

Lopinto, C., Young, W. B. & Ashkenazi, A. 2006. Comparison of dynamic (brush) and static (pressure) mechanical allodynia in migraine. *Cephalalgia,* 26**,** 852-856.

Lord, J. A., Waterfield, A. A., Hughes, J. & Kosterlitz, H. W. 1977. Endogenous opioid peptides: multiple agonists and receptors. *Nature,* 267**,** 495-499.

Lu, Q., Peevey, J., Jow, F., Monaghan, M. M., Mendoza, G., Zhang, H., Wu, J., Kim, C. Y., Bicksler, J., Greenblatt, L., Lin, S. S., Childers, W. & Bowlby, M. R. 2008. Disruption of Kv1.1 N-type inactivation by novel small molecule inhibitors (disinactivators). *Bioorganic & Medicinal Chemistry,* 16**,** 3067-3075.

Lubinska, L. 1977. Early course of Wallerian degeneration in myelinated fibres of the rat phrenic nerve. *Brain Research,* 130**,** 47-63.

Luo, Z. D., Chaplan, S. R., Higuera, E. S., Sorkin, L. S., Stauderman, K. A., Williams, M. E. & Yaksh, T. L. 2001. Upregulation of dorsal root ganglion (alpha)2(delta) calcium channel subunit and its correlation with allodynia in spinal nerve-injured rats. *Journal of Neuroscience,* 21**,** 1868-1875.

Ma, W. & Eisenach, J. C. 2003. Chronic constriction injury of sciatic nerve induces the up-regulation of descending inhibitory noradrenergic innervation to the lumbar dorsal horn of mice. *Brain Research.* , 970**,** 110-118.

Marchettini, P. 1993. Muscle pain: animal and human experimental and clinical studies. *Muscle Nerve,* 16**,** 1033-1039.

Marchettini, P., Lacerenza, M., Mauri, E. & Marangoni, C. 2006. Painful Peripheral Neuropathies. *Current Neuropharmacology,* 4**,** 175-181.

Martini, R., Fischer, S., Lopez-Vales, R. & David, S. 2008. Interactions between Schwann cells and macrophages in injury and inherited demyelinating disease. *Glia,* 56**,** 1566-1577.

Maves, T. J., Pechman, P. S., Gebhart, G. F. & Meller, S. T. 1993. Possible chemical contribution from chromic gut sutures produces disorders of pain sensation like those seen in man. *Pain,* 54**,** 57-69.

Mcdiarmid, T., Mackler, L. & Schneider, D. M. 2005. Clinical inquiries. What is the addiction risk associated with tramadol? *Journal of Family Practice,* 54**,** 72-73.

Mcdonald, J. & Lambert, D. 2005. Opioid receptors. *Continuing Education in Anaesthesia, Critical Care & Pain,* 5**,** 22-25.

Mckeown, L., Swanton, L., Robinson, P. & Jones, O. T. 2008. Surface expression and distribution of voltage-gated potassium channels in neurons (Review). *Molecular Membrane Biology,* 25**,** 332-343.

Mclachlan, E. M., Janig, W., Devor, M. & Michaelis, M. 1993. Peripheral nerve injury triggers noradrenergic sprouting within dorsal root ganglia. *Nature,* 363**,** 543-546.

Meller, S. T. & Gebhart, G. F. 1993. Nitric oxide (NO) and nociceptive processing in the spinal cord. *Pain,* 52**,** 127-136.

Merrer, J. L., Becker, J. a. J., Befort, K. & Kieffer, B. L. 2009. Reward Processing by the Opioid System in the Brain. *Physiological Reviews,* 89**,** 1379-1412.

Merskey, H. & Bogduk, N. 1994. A Current List with Definitions and Notes on Usage. IASP Task Force on Taxonomy. IASP Press, Seattle.

Metz, A. E., Yau, H. J., Centeno, M. V., Apkarian, A. V. & Martina, M. 2009. Morphological and functional reorganization of rat medial prefrontal cortex in neuropathic pain. *Proceedings of the National Academy of Sciences of the United States of America,* 106**,** 2423-2428.

Meyer, R. D. & Antonini, C. J. 1989. A review of suture materials, Part II. *Compendium,* 10**,** 360-362, 364, 366-368.

Mi, H., Deerinck, T. J., Ellisman, M. H. & Schwarz, T. L. 1995. Differential distribution of closely related potassium channels in rat Schwann cells. *Journal of Neuroscience,* 15**,** 3761-3774.

Min, J. H., Park, C. M., Moon, D. E., Kim, S. N., Chung, C. W. & Kim, K. H. 2001. Fos Expression in the Brain of Neuropathic Pain Rats. *Korean Journal of Anesthesiology,* 41**,** 229-238.

Minamimoto, T. & Kimura, M. 2002. Participation of the thalamic CM-Pf complex in attentional orienting. *Journal of Neurophysiology,* 87**,** 3090-3101.

Ming-Tatt, L., Khalivulla, S. I., Akhtar, M. N., Lajis, N., Perimal, E. K., Akira, A., Ali, D. I. & Sulaiman, M. R. 2013. Anti-hyperalgesic effect of a benzilidine-cyclohexanone analogue on a mouse model of chronic constriction injury-induced neuropathic pain: Participation of the κ-opioid receptor and KATP. *Pharmacology, Biochemistry and Behavior,* 114-115**,** 58-63.

Moalem, G. & Tracey, D. J. 2006. Immune and inflammatory mechanisms in neuropathic pain. *Brain Research Reviews,* 51**,** 240-264.

Mogil, J. S. & Crager, S. E. 2004. What should we be measuring in behavioral studies of chronic pain in animals? *Pain,* 112**,** 12-15.

Molander, C., Hongpaisan, J. & Grant, G. 1992. Changing pattern of c-FOS expression in spinal cord neurons after electrical stimulation of the chronically injured sciatic nerve in the rat. *Neuroscience,* 50**,** 223-236.

Monnikes, H., Ruter, J., Konig, M., Grote, C., Kobelt, P., Klapp, B. F., Arnold, R., Wiedenmann, B. & Tebbe, J. J. 2003. Differential induction of c-fos expression in brain nuclei by noxious and non-noxious colonic distension: role of afferent C-fibers and 5-HT3 receptors. *Brain Research,* 966**,** 253-264.

Moore, K. A., Kohno, T., Karchewski, L. A., Scholz, J., Baba, H. & Woolf, C. J. 2002. Partial peripheral nerve injury promotes a selective loss of GABAergic inhibition in the superficial dorsal horn of the spinal cord. *Journal of Neuroscience,* 22**,** 6724-6731.

Morgan, J. I. & Curran, T. 1991. Stimulus-transcription coupling in the nervous system: involvement of the inducible proto-oncogenes fos and jun. *Annual Review of Neuroscience,* 14**,** 421-451.

Morland, R. H., Novejarque, A., Spicer, C., Pheby, T. & Rice, A. S. C. 2016. Enhanced c-Fos expression in the central amygdala correlates with increased thigmotaxis in rats with peripheral nerve injury. *European Journal of Pain,* 20**,** 1140-1154.

Moseley, G. L. & Flor, H. 2012. Targeting cortical representations in the treatment of chronic pain: a review. *Neurorehabilitation and Neural Repair,* 26**,** 646-652.

Moulin, D. E., Clark, A. J., Gilron, I., Ware, M. A., Watson, C. P. N., Sessle, B. J., Coderre, T., Morley-Forster, P. K., Stinson, J., Boulanger, A., Peng, P., Finley, G. A., Taenzer, P., Squire, P., Dion, D., Cholkan, A., Gilani, A., Gordon, A., Henry, J., Jovey, R., Lynch, M., Mailis-Gagnon, A., Panju, A., Rollman, G. B. & Velly, A. 2007. Pharmacological management of chronic neuropathic pain – Consensus statement and guidelines from the Canadian Pain Society. *Pain Research & Management : The Journal of the Canadian Pain Society,* 12**,** 13-21.

Moulin, D. E., Palma, D., Watling, C. & Schulz, V. 2005. Methadone in the Management of Intractable Neuropathic Noncancer Pain. *Canadian Journal of Neurological Sciences / Journal Canadien des Sciences Neurologiques,* 32**,** 340-343.

Mueller, M., Wacker, K., Ringelstein, E. B., Hickey, W. F., Imai, Y. & Kiefer, R. 2001. Rapid response of identified resident endoneurial macrophages to nerve injury. *American Journal of Pathology,* 159**,** 2187-2197.

Mukherjee, D., Singh, C. B., Dey, S., Mandal, S., Ghosh, J., Mallick, S., Hussain, A., Swapana, N., Ross, S. A. & Pal, C. 2016. Induction of apoptosis by zerumbone isolated from Zingiber zerumbet (L.) Smith in protozoan parasite Leishmania

donovani due to oxidative stress. *The Brazilian Journal of Infectious Diseases,* 20**,** 48-55.

Munglani, R. & Hunt, S. P. 1995. Molecular biology of pain. *Br J Anaesth,* 75**,** 186-192.

Murakami, A., Hayashi, R., Takana, T., Kwon, K. H., Ohigashi, H. & R, S. 2003. Suppression of dextran sodium sulfateinduced colitis in mice by zerumbone, a subtropical ginger sesquiterpene, and nimesulide: separately and in combination. *Biochemical Pharmacology,* 66**,** 1253-1261.

Murakami, A. & Ohigashi, H. 2006. Cancer-preventive anti-oxidants that attenuate free radical generation by inflammatory cells. *Biological Chemistry,* 387**,** 387-392.

Murakami, A., Takahashi, D., Kinoshita, T., Koshimizu, K., Kim, H., W. & Yoshihiro, A. 2002. Zerumbone, a Southeast Asian ginger sesquiterpene, markedly suppresses free radical generation, proinflammatory protein production, and cancer cell proliferation accompanied by apoptosis: the a,b-unsaturated carbonyl group is a prerequisite. *Carcinogenesis,* 23**,** 795-802.

Murphy, P. G., Ramer, M. S., Borthwick, L., Gauldie, J., Richardson, P. M. & Bisby, M. A. 1999. Endogenous interleukin-6 contributes to hypersensitivity to cutaneous stimuli and changes in neuropeptides associated with chronic nerve constriction in mice. *European Journal of Neuroscience,* 11**,** 2243-2253.

Myles, L. M. & Glasby, M. A. 1991. Recovery of nerve function after repair of the sciatic nerve in the rat. Neuro-Orthopedics. *Neuro-Orthopedics,* 12**,** 65-85.

Nadal, X., Banos, J. E., Kieffer, B. L. & Maldonado, R. 2006. Neuropathic pain is enhanced in delta-opioid receptor knockout mice. *European Journal of Neuroscience,* 23**,** 830-834.

Nalawade, S. M., Sagare, A. P., Lee, C. Y., Kao, C. L. & Tsay., H. S. 2003. Studies on tissue culture of Chinese medicinal plant resources in Taiwan and their sustainable utilization. *Botanical Bulletin of Academia Sinica,* 44**,** 79-98.

Namaka, M., Gramlich, C. R., Ruhlen, D., Melanson, M., Sutton, I. & Major, J. 2004. A treatment algorithm for neuropathic pain. *Clinical Therapeutics,* 26**,** 951-979.

Narita, M., Imai, S., Oe, K., Narita, M., Kubota, C., Yajima, Y., Yamazaki, Y., Yamazaki, M. & Suzuki, T. 2004. Induction of c-fos expression in the mouse brain associated with hyperalgesia induced by intrathecal injection of protein kinase activator. *Brain Research,* 1015**,** 189-193.

Narita, M., Niikura, K., Nanjo-Niikura, K., Narita, M., Furuya, M., Yamashita, A., Saeki, M., Matsushima, Y., Imai, S., Shimizu, T., Asato, M., Kuzumaki, N., Okutsu, D., Miyoshi, K., Suzuki, M., Tsukiyama, Y., Konno, M., Yomiya, K., Matoba, M. & Suzuki, T. 2011. Sleep disturbances in a neuropathic pain-like condition in the mouse are associated with altered GABAergic transmission in the cingulate cortex. *Pain,* 152**,** 1358-1372.

Narita, M., Ozaki, S., Narita, M., Ise, Y., Yajima, Y. & Suzuki, T. 2003a. Change in the expression of c-fos in the rat brain following sciatic nerve ligation. *Neuroscience letters.,* 352**,** 231-233.

Narita, M., Ozaki, S., Narita, M., Ise, Y., Yajima, Y. & Suzuki, T. 2003b. Change in the expression of c-fos in the rat brain following sciatic nerve ligation. *Neuroscience Letters,* 352**,** 231-233.

Nathan, C. 2006. Neutrophils and immunity: challenges and opportunities. *Nature Reviews Immunology,* 6**,** 173-182.

Nejad, S. H., Alpay, M., Stern, T., Fricchione, G., Cassem, G., Jellinek, M. & Rosenbaum, J. 2010. Pain patients. *MGH Handbook of General Hospital Psychiatry, Saunders, Washington DC***,** 211-236.

Neugebauer, V., Galhardo, V., Maione, S. & Mackey, S. C. 2009. Forebrain pain mechanisms. *Brain Research Reviews,* 60**,** 226-242.

Neugebauer, V. & Li, W. 2001. Processing of nociceptive mechanical and thermal information in central amygdala neurons with knee-joint input. *Journal of Neurophysiology,* 87**,** 103-112.

Nickel, F. T., Seifert, F., Lanz, S. & Maihofner, C. 2012. Mechanisms of neuropathic pain. *European Neuropsychopharmacology,* 22**,** 81-91.

Ning, L., Ma, L. Q., Wang, Z. R. & Wang, Y. W. 2013. Chronic constriction injury induced long-term changes in spontaneous membrane-potential oscillations in anterior cingulate cortical neurons in vivo. *Pain Physician,* 16**,** E577-589.

O'connor, A. B. 2009. Neuropathic pain: quality-of-life impact, costs and cost effectiveness of therapy. *Pharmacoeconomics,* 27**,** 95-112.

Ocana, M. & Baeyens, J. M. 1993. Differential effects of K+ channel blockers on antinociception induced by alpha 2-adrenoceptor, GABAB and kappa-opioid receptor agonists. *British Journal of Pharmacology,* 110**,** 1049-1054.

Ocana, M., Cendan, C. M., Cobos, E. J., Entrena, J. M. & Baeyens, J. M. 2004. Potassium channels and pain: present realities and future opportunities. *European Journal of Pharmacology,* 500**,** 203-219.

Ocana, M., Del Pozo, E., Barrios, M., Robles, L. I. & Baeyens, J. M. 1990. An ATP-dependent potassium channel blocker antagonizes morphine analgesia. *European Journal of Pharmacology,* 186**,** 377-378.

Ogunwande, I. A., Olawore, N. O. & Adeleke, K. A. 2005. Contribution to the Study of Essential Oil of Xylopia Aethiopica (DUNAL) A. RICH: Isolation and Characterization of Zerumbone. *Journal of Essential Oil Bearing Plants,* 8**,** 159-164.

Ohtori, S., Miyagi, M., Eguchi, Y., Inoue, G., Orita, S., Ochiai, N., Kishida, S., Kuniyoshi, K., Nakamura, J., Aoki, Y., Ishikawa, T., Arai, G., Kamoda, H., Suzuki, M., Takaso, M., Furuya, T., Kubota, G., Sakuma, Y., Oikawa, Y., Toyone, T. & Takahashi, K. 2012a. Efficacy of epidural administration of anti-interleukin-6 receptor antibody onto spinal nerve for treatment of sciatica. *European Spine Journal,* 21**,** 2079-2084.

Ohtori, S., Miyagi, M., Eguchi, Y., Inoue, G., Orita, S., Ochiai, N., Kishida, S., Kuniyoshi, K., Nakamura, J., Aoki, Y., Ishikawa, T., Arai, G., Kamoda, H., Suzuki, M., Takaso, M., Furuya, T., Toyone, T. & Takahashi, K. 2012b. Epidural administration of spinal nerves with the tumor necrosis factor-alpha inhibitor, etanercept, compared with dexamethasone for treatment of sciatica in patients with lumbar spinal stenosis: a prospective randomized study. *Spine (Phila Pa 1976),* 37**,** 439-444.

Okamoto, K., Martin, D. P., Schmelzer, J. D., Mitsui, Y. & Low, P. A. 2001. Pro- and anti-inflammatory cytokine gene expression in rat sciatic nerve chronic constriction injury model of neuropathic pain. *Experimental Neurology,* 169**,** 386-391.

Oliveira Júnior, J. O. D., Portella Junior, C. S. A. & Cohen, C. P. 2016. Inflammatory mediators of neuropathic pain. *Revista Dor,* 17**,** 35-42.

Ortega-Legaspi, J. M., Lopez-Avila, A., Coffeen, U., Del Angel, R. & Pellicer, F. 2003. Scopolamine into the anterior cingulate cortex diminishes nociception in a neuropathic pain model in the rat: an interruption of 'nociception-related memory acquisition'? *European Journal of Pharmacology,* 7**,** 425-429.

Ossipov, M. H., Morimura, K. & Porreca, F. 2014. Descending pain modulation and chronification of pain. *Current Opinion in Supportive and Palliative Care,* 8**,** 143-151.

Othman, N., Cardosa, M. & Jamil, Z. O. 2011. Establishing a pain clinic in a developing country- a Malaysian experience based on 10 years data (2000-2010). *Poster presented at ASEAPS 2011; May 5-8, Pattaya, Thailand*.

Palmer, M. T. & Weaver, C. T. 2010. Autoimmunity: increasing suspects in the CD4+ T cell lineup. *Nature Immunology,* 11**,** 36-40.

Park, E. S., Gao, X., Chung, J. M. & Chung, K. 2006a. Levels of mitochondrial reactive oxygen species increase in rat neuropathic spinal dorsal horn neurons. *Neuroscience Letters,* 391**,** 108-111.

Park, S. I., Oh, J. H., Hwang, Y. S., Kim, S. J. & Chang, J. W. 2006b. Electrical stimulation of the anterior cingulate cortex in a rat neuropathic pain model. *Acta Neurochirurgica Supplement,* 99**,** 65-71.

Passmore, G. M., Selyanko, A. A., Mistry, M., Al-Qatari, M., Marsh, S. J., Matthews, E. A., Dickenson, A. H., Brown, T. A., Burbidge, S. A., Main, M. & Brown, D. A. 2003. KCNQ/M currents in sensory neurons: significance for pain therapy. *Journal of Neuroscience,* 23**,** 7227-7236.

Pathak, K. & Raghuvanshi, S. 2015. Oral bioavailability: issues and solutions via nanoformulations. *Clinical Pharmacokinetics,* 54**,** 325-357.

Paxinos, G. & Franklin, K. B. J. 1997. The Mouse Brain in Stereotaxic Coordinates. *Academic Press, San Diego*.

Perimal, E. K., Akhtar, M. N., Mohamad, A. S., Khalid, M. H., Ong, H. M., Khalid, S., Lee, M. T., Kamaldin, M. N., Zakaria, Z. A., Israf, D. A., Lajis, N. & Sulaiman, M. R. 2011. Zerumbone-induced antinociception: involvement of the L-Arginine-Nitric Oxide-cGMP -PKC-K+ATP Channel Pathways. *Basic & Clinical Pharmacology & Toxicology,* 108**,** 155-162.

Perrin, F. E., Lacroix, S., Avilés-Trigueros, M. & David, S. 2005. Involvement of monocyte chemoattractant protein-1, macrophage inflammatory protein-1α and interleukin-1β in Wallerian degeneration. *Brain,* 128**,** 854-866.

Pertovaara, A. & Almeida, A. 2006. Descending inhibitory systems. *Handbook of Clinical Neurology,* 81**,** 179-192.

Pezet, S. & Mcmahon, S. B. 2006. Neurotrophins: mediators and modulators of pain. *Annual Review of Neuroscience,* 29**,** 507-538.

Prakash, R. O., Rabinarayan, A. & Kumar, M. S. 2011. Zingiber zerumbet (L.) Sm., a reservoir plant for therapeutic uses: a review. *International Journal of Research in Ayurveda and Pharmacy,* 2**,** 1-22.

Prasad, S., Sung, B. & Aggarwal, B. B. 2012. Age-associated chronic diseases require age-old medicine: role of chronic inflammation. *Preventive Medicine,* 54 Suppl**,** S29-37.

Prasad, S. & Tyagi, A. K. 2015. Ginger and Its Constituents: Role in Prevention and Treatment of Gastrointestinal Cancer. *Gastroenterology Research and Practice,* 2015**,** 11.

Prasannan, R., Kalesh, K. A., Shanmugam, M. K., Nachiyappan, A., Ramachandran, L., Nguyen, A. H., Kumar, A. P., Lakshmanan, M., Ahn, K. S. & Sethi, G. 2012. Key cell signaling pathways modulated by zerumbone: role in the prevention and treatment of cancer. *Biochemical Pharmacology,* 84**,** 1268-1276.

Presley, R. W., Menetrey, D., Levine, J. D. & Basbaum, A. I. 1990. Systemic morphine suppresses noxious stimulus-evoked Fos protein-like immunoreactivity in the rat spinal cord. *Journal of Neuroscience,* 70**,** 323-335.

Radat, F., Margot-Duclot, A. & Attal, N. 2013. Psychiatric co-morbidities in patients with chronic peripheral neuropathic pain: a multicentre cohort study. *European Journal of Pharmacology,* 17**,** 1547-1557.

Raffa, R. B. & Martinez, R. P. 1995. The 'glibenclamide-shift' of centrally-acting antinociceptive agents in mice. *Brain Research,* 677**,** 277-282.

Rahman, H. S., Rasedee, A., How, C. W., Abdul, A. B., Zeenathul, N. A., Othman, H. H., Saeed, M. I. & Yeap, S. K. 2013. Zerumbone-loaded nanostructured lipid carriers: preparation, characterization, and antileukemic effect. *International Journal of Nanomedicine,* 8**,** 2769-2781.

Rahman, H. S., Rasedee, A., Yeap, S. K., Othman, H. H., Chartrand, M. S., Namvar, F., Abdul, A. B. & How, C. W. 2014. Biomedical properties of a natural dietary plant metabolite, zerumbone, in cancer therapy and chemoprevention trials. *BioMed Research International,* 2014**,** 920742.

Rahmani, A. H., Shabrmi, F. M. A. & Aly, S. M. 2014. Active ingredients of ginger as potential candidates in the prevention and treatment of diseases via modulation of biological activities. *International Journal of Physiology, Pathophysiology and Pharmacology,* 6**,** 125-136.

Raja, S. N., Haythornthwaite, J. A., Pappagallo, M., Clark, M. R., Travison, T. G., Sabeen, S., Royall, R. M. & Max, M. B. 2002. Opioids versus antidepressants in postherpetic neuralgia: a randomized, placebo-controlled trial. *Neurology,* 59**,** 1015-1021.

Ramabadran, K., Bansinath, M., Turndorf, H. & Puig, M. M. 1989. Tail immersion test for the evaluation of a nociceptive reaction in mice. Methodological considerations. *Journal of Pharmacological Methods,* 21**,** 21-31.

Ramer, M. S., Kawaja, M. D., Henderson, J. T., Roder, J. C. & Bisby, M. A. 1998a. Glial overexpression of NGF enhances neuropathic pain and adrenergic sprouting into DRG following chronic sciatic constriction in mice. *Neuroscience Letters,* 251**,** 53-56.

Ramer, M. S., Murphy, P. G., Richardson, P. M. & Bisby, M. A. 1998b. Spinal nerve lesion-induced mechanoallodynia and adrenergic sprouting in sensory ganglia are attenuated in interleukin-6 knockout mice. *Pain,* 78**,** 115-121.

Randall, L. O. & Selitto, J. J. 1957. cA method for measurement of analgesic activity on inflamed tissue. *Archives Internationales de Pharmacodynamieet de therapie,* 111**,** 409-419.

Rasband, M. N., Trimmer, J. S., Schwarz, T. L., Levinson, S. R., Ellisman, M. H., Schachner, M. & Shrager, P. 1998. Potassium channel distribution, clustering, and function in remyelinating rat axons. *Journal of Neuroscience,* 18**,** 36-47.

Rashid, R. A. & Pihie, A. H. 2005. The antiproliferative effects of Zingiber zerumbet extracts and fractions on the growth of human breast carcinoma cell lines. *Malaysian Journal of Pharmaceutical Sciences,* 3**,** 45-52.

Rates, S. M. K. 2001. Plants as source of drugs. *Toxicon,* 39**,** 603-613.

Reddi, D. D., Curran, D. N. & Stephens, D. R. 2013. An introduction to pain pathways and mechanisms. *British Journal of Hospital Medicine,* 74**,** C188-C191.

Ren, K. & Dubner, R. 1999. Inflammatory Models of Pain and Hyperalgesia. *Ilar j,* 40**,** 111-118.

Ren, W.-J., Liu, Y., Zhou, L.-J., Li, W., Zhong, Y., Pang, R.-P., Xin, W.-J., Wei, X.-H., Wang, J., Zhu, H.-Q., Wu, C.-Y., Qin, Z.-H., Liu, G. & Liu, X.-G. 2011. Peripheral Nerve Injury Leads to Working Memory Deficits and Dysfunction of the Hippocampus by Upregulation of TNF-α in Rodents. *Neuropsychopharmacology,* 36**,** 979-992.

Ressler, K. J. 2010. Amygdala activity, fear, and anxiety: modulation by stress. *Biological Psychiatry,* 67**,** 1117-1119.

Rhode, J., Fogoros, S., Zick, S., Wahl, H., Griffith, K. A., Huang, J. & Liu, J. R. 2007. Ginger inhibits cell growth and modulates angiogenic factors in ovarian cancer cells. *BMC Complementary and Alternative Medicine,* 7**,** 44.

Ringkamp, M. & Raja, S. N. 2014. A sore spot: central or peripheral generation of chronic neuropathic spontaneous pain? *Pain,* 155**,** 1189-1191.

Robinson, I. & Meert, T. F. 2005. Stability of neuropathic pain symptoms in partial sciatic nerve ligation in rats is affected by suture material. *Neuroscience Letters,* 373**,** 125-129.

Robles, L. I., Barrios, M., Del Pozo, E., Dordal, A. & Baeyens, J. M. 1996. Effects of K+ channel blockers and openers on antinociception induced by agonists of 5-HT1A receptors. *European Journal of Pharmacology,* 295**,** 181-188.

Roche, A. K., Cook, M., Wilcox, G. L. & Kajander, K. C. 1996. A nitric oxide synthesis inhibitor (L-NAME) reduces licking behavior and Fos-labeling in the spinal cord of rats during formalin-induced inflammation. *Pain,* 66**,** 331-341.

Rose, K., Ooi, L., Dalle, C., Robertson, B., Wood, I. C. & Gamper, N. 2011. Transcriptional repression of the M channel subunit Kv7.2 in chronic nerve injury. *Pain,* 152**,** 742-754.

Rosenblum, A., Marsch, L. A., Joseph, H. & Portenoy, R. K. 2008. Opioids and the Treatment of Chronic Pain: Controversies, Current Status, and Future Directions. *Experimental and Clinical Psychopharmacology,* 16**,** 405-416.

Rotshenker, S. 2011. Wallerian degeneration: the innate-immune response to traumatic nerve injury. *Journal of Neuroinflammation,* 8**,** 109-109.

Rout, K., Mishra, S. & Sherma, J. 2009. Development and validation of an HPTLC method for analysis of zerumbone, the anticancer marker from Zingiber zerumbet. *Acta Chromatographica,* 21**,** 443-452.

Ruiz-Garcia, A., Bermejo, M., Moss, A. & Casabo, V. G. 2008. Pharmacokinetics in drug discovery. *Journal of Pharmaceutical Sciences,* 97**,** 654-690.

Ruslay, S., Abas, F., Shaari, K., Zainal, Z., Maulidiani, Sirat, H., Israf, D. A. & Lajis, N. H. 2007. Characterization of the components present in the active fractions of health gingers (Curcuma xanthorrhiza and Zingiber zerumbet) by HPLC–DAD–ESIMS. *Food Chemistry,* 104**,** 1183-1191.

Sabu, M. 2003. Revision of the genus Zingiber in South India. *Folia Malaysiana,* 4**,** 25-52.

Sacerdote, P., Franchi, S., Trovato, A. E., Valsecchi, A. E., Panerai, A. E. & Colleoni, M. 2008. Transient early expression of TNF-alpha in sciatic nerve and dorsal root ganglia in a mouse model of painful peripheral neuropathy. *Neuroscience Letters,* 436**,** 210-213.

Sahebkar, A. 2011. Potential efficacy of ginger as a natural supplement for nonalcoholic fatty liver disease. *World Journal of Gastroenterology : WJG,* 17**,** 271-272.

Saitoh, A., Sugiyama, A., Nemoto, T., Fujii, H., Wada, K., Oka, J., Nagase, H. & Yamada, M. 2011. The novel delta opioid receptor agonist KNT-127 produces antidepressant-like and antinociceptive effects in mice without producing convulsions. *Behavioural Brain Research,* 223**,** 271-279.

Salgado, C., Vilson, F., Miller, N. R. & Bernstein, S. L. 2011. Cellular inflammation in nonarteritic anterior ischemic optic neuropathy and its primate model. *Archives of Ophthalmology,* 129**,** 1583-1591.

Sandkühler, J. 2009. Models and mechanisms of hyperalgesia and allodynia. *Physiological Reviews,* 89**,** 707-758.

Sansone, R. A. & Sansone, L. A. 2009. Tramadol: Seizures, Serotonin Syndrome, and Coadministered Antidepressants. *Psychiatry (Edgmont),* 6**,** 17-21.

Santos-Nogueira, E., Redondo Castro, E., Mancuso, R. & Navarro, X. 2012. Randall-Selitto Test: A New Approach for the Detection of Neuropathic Pain after Spinal Cord Injury. *Journal of Neurotrauma,* 29**,** 898-904.

Sapolsky, R. M. 2003. Stress and Plasticity in the Limbic System. *Neurochemical Research,* 28**,** 1735-1742.

Sarantopoulos, C. D., Mccallum, J. B., Rigaud, M., Fuchs, A., Kwok, W. M. & Hogan, Q. H. 2007. Opposing effects of spinal nerve ligation on calcium-activated potassium currents in axotomized and adjacent mammalian primary afferent neurons. *Brain Research,* 1132**,** 84-99.

Savjani, K. T., Gajjar, A. K. & Savjani, J. K. 2012. Drug Solubility: Importance and Enhancement Techniques. *ISRN Pharmaceutics,* 2012**,** 195727.

Scholz, J. & Woolf, C. J. 2007. The neuropathic pain triad: neurons, immune cells and glia. *Nature Neuroscience,* 10**,** 1361-1368.

Schulze, D., Krauter, T., Fritzenschaft, H., Soom, M. & Baukrowitz, T. 2003. Phosphatidylinositol 4,5-Bisphosphate (PIP2) Modulation of ATP and pH Sensitivity in Kir Channels: A Tale Of An Active And A Silent Pip2 Site In The N Terminus. *Journal of Biological Chemistry,* 278**,** 10500-10505.

Seino, S. & Miki, T. 2003. Physiological and pathophysiological roles of ATP-sensitive K+ channels. *Progress in Biophysics & Molecular Biology,* 81**,** 133-176.

Sekiguchi, F., Mita, Y., Kamanaka, Y., Kawao, N., Matsuya, H., Taga, C. & Kawabata, A. 2004. The potent inducible nitric oxide synthase inhibitor ONO- 1714 inhibits neuronal NOS and exerts antinociception in rats. *Neuroscience Letters,* 365**,** 111-115.

Seltzer, Z., Dubner, R. & Shir, Y. 1990. A novel behavioral model of neuropathic pain disorders produced in rats by partial sciatic nerve injury. *Pain,* 43**,** 205-218.

Selvarajah, D., Cash, T., Sankar, A., Thomas, L., Davies, J., Cachia, E., Gandhi, R., Wilkinson, I. D., Wilkinson, N., Emery, C. J. & Tesfaye, S. 2014. The contributors of emotional distress in painful diabetic neuropathy. *Diabetes and Vascular Disease Research,* 11**,** 218-225.

Sgambato, V., Abo, V., Rogard, M., Besson, M. J. & Deniau, J. M. 1997. Effect of electrical stimulation of the cerebral cortex on the expression of the Fos protein in the basal ganglia. *Neuroscience,* 81**,** 93-112.

Shaji, J. & Patole, V. 2008. Protein and Peptide drug delivery: oral approaches. *Indian Journal of Pharmaceutical Sciences,* 70**,** 269-277.

Shanks, N., Greek, R. & Greek, J. 2009. Are animal models predictive for humans? *Philosophy, Ethics, and Humanities in Medicine,* 4**,** 2.

Sharma, I., Gusain, D. & Dixit, V. P. 1996. Hypolipidemic and antiatherosclerotic effect of Zingiber officinale in cholesterol fed rabbits. *Phytotherapy Research,* 10**,** 517-518.

Sheen, K. & Chung, J. M. 1993. Signs of neuropathic pain depend on signals from injured nerve fibers in a rat model. *Brain Research,* 610**,** 62-68.

Shen, L. F., Cheng, H., Tsai, M. C., Kuo, H. S. & Chak, K. F. 2009. PAL31 may play an important role as inflammatory modulator in the repair process of the spinal cord injury rat. *Journal of Neurochemistry,* 108**,** 1187-1197.

Shen, Z. L., Lassner, F., Bader, A., Becker, M., Walter, G. F. & Berger, A. 2000. Cellular activity of resident macrophages during Wallerian degeneration. *Microsurgery,* 20**,** 255-261.

Shimoyama, M., Tanaka, K., Hasua, F. & Shimoyama, N. 2002. A mouse model of neuropathic cancer pain. *Pain,* 99**,** 167-174.

Shipton, E. 2008. Post-surgical neuropathic pain. *ANZ Journal of Surgery,* 78**,** 548-555.

Shukla, Y. & Singh, M. 2007. Cancer preventive properties of ginger: a brief review. *Food and Chemical Toxicology,* 45**,** 683-690.

Sidahmed, H. M. A., Hashim, N. M., Abdulla, M. A., Ali, H. M., Mohan, S., Abdelwahab, S. I., Taha, M. M. E., Fai, L. M. & Vadivelu, J. 2015. Antisecretory, Gastroprotective, Antioxidant and Anti-Helicobcter Pylori Activity of Zerumbone from Zingiber Zerumbet (L.) Smith. *PLoS ONE,* 10**,** e0121060.

Siddiqui, A. A., Iram, F., Siddiqui, S. & Sahu, K. 2014. Role of Natural Products in Drug Discovery Process *International Journal of Drug Development and Research,* 6**,** 172-204.

Sigworth, F. J. 1994. Voltage gating of ion channels. *Quarterly Reviews of Biophysics,* 27**,** 1-40.

Sikes, R. W. & Vogt, B. A. 1992. Nociceptive neurons in area 24 of rabbit cingulate cortex. *Journal of Neurophysiology,* 68**,** 1720-1732.

Silva, A. C., Santos, D., Ferreira, D. & Lopes, C. M. 2012. Lipid-based nanocarriers as an alternative for oral delivery of poorly water- soluble drugs: peroral and mucosal routes. *Current Medicinal Chemistry,* 19**,** 4495-4510.

Simons, L. E., Moulton, E. A., Linnman, C., Carpino, E., Becerra, L. & Borsook, D. 2014. The human amygdala and pain: evidence from neuroimaging. *Human Brain Mapping,* 35**,** 527-538.

Singewald, N., Salchner, P. & Sharp, T. 2003. Induction of c-Fos expression in specific areas of the fear circuitry in rat forebrain by anxiogenic drugs. *Biological Psychiatry,* 53**,** 275-283.

Siqueira Mietto, B., Kroner, A., Girolami, E. I., Santos-Nogueira, E., Zhang, J. & David, S. 2015. Role of IL-10 in Resolution of Inflammation and Functional Recovery after Peripheral Nerve Injury. *The Journal of Neuroscience,* 35**,** 16431-16442.

Sirat, H. M. & Nordin, A. B. 1994. Essential oil of Zingiber ottensii valeton. *Journal of Essential Oil Research,* 6**,** 635-636.

Smith, H. S. 2012. Opioids and neuropathic pain. *Pain Physician,* 15**,** 93-110.

Soleimannejad, E., Semnanian, S., Fathollahi, Y. & Naghdi, N. 2006. Microinjection of ritanserin into the dorsal hippocampal CA1 and gyrus decrease nociceptive behavior in adult male rat. *Behavioural Brain Research,* 168**,** 221-225.

Somchit, M. N., Mak, J. H., Bustamam, A. A., Zuraini, A., Arifah, A. K., Adam, Y. & Zakaria, Z. A. 2012. Zerumbone isolated from Zingiber zerumbet inhibits inflammation and pain in rats. *Journal of Medicinal Plants Research,* 6**,** 177-180.

Somchit, M. N., Shukriyah, M. H., Bustamam, A. A. & Zuraini, A. 2005. Anti-pyretic and analgesic activity of Zingiber zerumbet. *International Journal of Pharmacology,* 1**,** 277-280.

Sommer, C. & Kress, M. 2004. Recent findings on how proinflammatory cytokines cause pain: peripheral mechanisms in inflammatory and neuropathic hyperalgesia. *Neuroscience Letters,* 361**,** 184-187.

Sommer, C., Petrausch, S., Lindenlaub, T. & Toyka, K. V. 1999. Neutralizing antibodies to interleukin 1-receptor reduce pain associated behavior in mice with experimental neuropathy. *Neuroscience Letters,* 270**,** 25-28.

Sommer, C. & Schafers, M. 1998. Painful mononeuropathy in C57BL/Wld mice with delayed wallerian degeneration: differential effects of cytokine production and nerve regeneration on thermal and mechanical hypersensitivity. *Brain Research,* 784**,** 154-162.

Souto, E. B., Wissing, S. A., Barbosa, C. M. & Muller, R. H. 2004. Development of a controlled release formulation based on SLN and NLC for topical clotrimazole delivery. *International Journal of Pharmaceutics,* 278**,** 71-77.

Soygüder, Z. 2004. NMDA and AMPA/KA receptors are involved in the c-Fos expression following mustard oil activation of C-fibres. *Journal of Chemical Neuroanatomy,* 28**,** 163-169.

Srivastava, A. K., Srivastava, S. K. & Shah, N. C. 2001. Constituents of the Rhizome Essential Oil of Curcuma amada Roxb. from India. *Journal of Essential Oil Research,* 13**,** 63-64.

Stirling, D. P. & Stys, P. K. 2010. Mechanisms of axonal injury: internodal nanocomplexes and calcium deregulation. *Trends in Molecular Medicine,* 16**,** 160-170.

Su, X., Castle, N. A., Antonio, B., Roeloffs, R., Thomas, J. B., Krafte, D. S. & Chapman, M. L. 2009. The effect of kappa-opioid receptor agonists on tetrodotoxin-resistant sodium channels in primary sensory neurons. *Anesthesia & Analgesia,* 109**,** 632-640.

Sulaiman, M. R., Perimal, E. K., Akhtar, M. N., Mohamad, A. S., Khalid, M. H., Tasrip, N. A., Mokhtar, F., Zakaria., Z. A., Lajis, N. H. & Israf, D. A. 2010. Anti-inflammatory effect of zerumbone on acute and chronic inflammation models in mice. *Fitoterapia,* 81**,** 855-858.

Sulaiman, M. R., Perimal, E. K., Zakaria, Z. A., Mokhtar, F., Akhtar, M., N. & Lajis, N. H. 2009. Preliminary analysis of the antinociceptive activity of zerumbone. *Fitoterapia,* 80**,** 230-232.

Sulaiman, O. A. & Gordon, T. 2000. Effects of short- and long-term Schwann cell denervation on peripheral nerve regeneration, myelination, and size. *Glia,* 32**,** 234-246.

Sulaiman, O. A. & Gordon, T. 2002. Transforming growth factor-beta and forskolin attenuate the adverse effects of long-term Schwann cell denervation on peripheral nerve regeneration in vivo. *Glia,* 37**,** 206-218.

Sultana, S., Ripa, F. A. & Hamid, K. 2010. Comparative antioxidant activity study of some commonly used spices in Bangladesh. *Pakistan Journal of Biological Sciences,* 13**,** 340-343.

Sun, W. Z., Shyu, B. C. & Shieh, J. Y. 1996. Nitrous oxide or halothane, or both, fail to suppress c-fos expression in rat spinal cord dorsal horn neurones after subcutaneous formalin. *British Journal of Anaesthesia,* 76**,** 99-105.

Sung, B., Murakami, A., Oyajobi, B. O. & Aggarwal, B. B. 2009. Zerumbone abolishes RaNKL-induced NF-kB activation, inhibits osteoclastogenesis, and suppresses human breast cancer-induced bone loss in athymic nude mice. *Cancer Research,* 69**,** 1477-1484.

Szabolcs, A., Tiszlavicz, L. & Kaszaki, J. E. A. 2007. "Zerumbone exerts a beneficial effect on inflammatory parameters of cholecystokinin octapeptide-induced experimental pancreatitis but fails to improve histology. *Pancreas,* 35**,** 249–255.

Taglialatela, M., Vandongen, A. M., Drewe, J. A., Joho, R. H., Brown, A. M. & Kirsch, G. E. 1991. Patterns of internal and external tetraethylammonium block in four homologous K+ channels. *Molecular Pharmacology,* 40**,** 299-307.

Takeda, R., Watanabe, Y., Ikeda, T., Abe, H., Ebihara, K., Matsuo, H., Nonaka, H., Hashiguchi, H., Nishimori, T. & Ishida, Y. 2009. Analgesic effect of milnacipran is associated with c-Fos expression in the anterior cingulate cortex in the rat neuropathic pain model. *Neuroscience Research,* 64**,** 380-384.

Tanaka, T., Shimizu, M., Kohno, H., Yoshitani, S., Tsukio, Y., Murakami, A., Safitri, R., Takahashi, D., Yamamoto, K., Koshimizu, K., Ohigashi, H. & Mori, H. 2001. Chemoprevention of azoxymethane-induced rat aberrant crypt foci by dietary zerumbone isolated from Zingiber zerumbet. *Life Sciences,* 69**,** 1935-1945.

Terada, M., Kuzumaki, N., Hareyama, N., Imai, S., Niikura, K., Narita, M., Yamazaki, M., Suzuki, T. & Narita, M. 2008. Suppression of enriched environment-induced neurogenesis in a rodent model of neuropathic pain. *Neuroscience letters,* 440**,** 314-318.

Tesfaye, S., Boulton, A. J. M. & Dickenson, A. H. 2013. Mechanisms and Management of Diabetic Painful Distal Symmetrical Polyneuropathy. *Diabetes Care,* 36**,** 2456-2465.

Tewtrakul, S. & Subhadhirasakul, S. 2007. Anti-allergic activity of some selected plants in the Zingiberaceae family. *Journal of Ethnopharmacology,* 109**,** 535-538.

Thing-Fong, T., Shorong-Shii, L., Chia Ju, C. & I-Min, L. 2013. Zerumbone, a tropical ginger sesquiterpene, ameliorates streptozotocin-induced diabetic nephropathy in rats by reducing the hyperglycemia-induced inflammatory response. *Nutrition & Metabolism,* 10**,** 64.

Thompson, J. M., Ji, G. & Neugebauer, V. 2015. Small-conductance calcium-activated potassium (SK) channels in the amygdala mediate pain-inhibiting effects of clinically available riluzole in a rat model of arthritis pain. *Molecular Pain,* 11**,** 51.

Torrance, N., Smith, B. H., Bennett, M. I. & Lee, A. J. 2006. The epidemiology of chronic pain of predominantly neuropathic origin. Results from a general population survey. *Journal of Pain,* 7**,** 281-289.

Torrecilla, M., Marker, C. L., Cintora, S. C., Stoffel, M., Williams, J. T. & Wickman, K. 2002. G-protein-gated potassium channels containing Kir3.2 and Kir3.3 subunits mediate the acute inhibitory effects of opioids on locus ceruleus neurons. *Journal of Neuroscience,* 22**,** 4328-4334.

Touma, E., Kato, S., Fukui, K. & Koike, T. 2007. Calpain-mediated cleavage of collapsin response mediator protein(CRMP)-2 during neurite degeneration in mice. *European Journal of Neuroscience,* 26**,** 3368-3381.

Treede, R.-D., Kenshalo, D. R., Gracely, R. H. & Jones, A. K. P. 1999. The cortical representation of pain. *Pain,* 79**,** 105-111.

Tsantoulas, C. & Mcmahon, S. B. 2014. Opening paths to novel analgesics: the role of potassium channels in chronic pain. *Trends in Neurosciences,* 37**,** 146-158.

Tsao, J. W., George, E. B. & Griffin, J. W. 1999. Temperature modulation reveals three distinct stages of Wallerian degeneration. *Journal of Neuroscience,* 19**,** 4718-4726.

Tsuboi, K., Matsuo, Y., Shamoto, T., Shibata, T., Koide, S., Morimoto, M., Guha, S., Sung, B., Aggarwal, B. B., Takahashi, H. & Takeyama, H. 2014. Zerumbone inhibits tumor angiogenesis via NF-κB in gastric cancer. *Oncology Report,* 3**,** 57-64.

Tyers, M. B. 1980. A classification of opiate receptors that mediate antinociception in animals. *British Journal of Pharmacology,* 69**,** 503-512.

Tzeng, T. F., Liou, S. S., Chang, C. J. & Liu, I. M. 2013. The Ethanol Extract of Zingiber zerumbet Attenuates Streptozotocin-Induced Diabetic Nephropathy in Rats. *Evidence-Based Complementary and Alternative Medicine,* 2013**,** 340645.

Ueda, H. & Rashid, M. H. 2003. Molecular Mechanisms of Neuropathic Pain. *Drug News Perspect,* 16**,** 605.

Upton, N., Sewell, R. D. & Spencer, P. S. 1983. Analgesic actions of mu- and kappa-opiate agonists in rats. *Archives internationales de pharmacodynamie et de therapie,* 262**,** 199-207.

Vadakkan, K. I., Jia, Y. H. & Zhuo, M. 2005. A behavioral model of neuropathic pain induced by ligation of the common peroneal nerve in mice. *Journal of Pain,* 6**,** 747-756.

Van Den Bergh, F. R. A., Vanhoenacker, F. M., De Smet, E., Huysse, W. & Verstraete, K. L. 2013. Peroneal nerve: Normal anatomy and pathologic findings on routine MRI of the knee. *Insights into Imaging,* 4**,** 287-299.

Van Der Wal, S., Cornelissen, L., Behet, M., Vaneker, M., Steegers, M. & Vissers, K. 2015. Behavior of neuropathic pain in mice following chronic constriction injury comparing silk and catgut ligatures. *SpringerPlus,* 4**,** 225.

Van Hecke, O., Austin, S. K., Khan, R. A., Smith, B. H. & Torrance, N. 2014. Neuropathic pain in the general population: a systematic review of epidemiological studies. *Pain,* 155**,** 654-662.

Vanderah, T. W. 2010. Delta and kappa opioid receptors as suitable drug targets for pain. *Clinical Journal of Pain,* 26**,** 10-15.

Vargas, M. E., Watanabe, J., Singh, S. J., Robinson, W. H. & Barres, B. A. 2010. Endogenous antibodies promote rapid myelin clearance and effective axon regeneration after nerve injury. *Proceedings of the National Academy of Sciences of the United States of America,* 107**,** 11993-11998.

Vergara, C., Latorre, R., Marrion, N. V. & Adelman, J. P. 1998. Calcium-activated potassium channels. *Current Opinion in Neurobiology,* 8**,** 321-329.

Vissers, K., De Jongh, R., Hoffmann, V., Heylen, R., Crul, B. & Meert, T. 2003. Internal and external factors affecting the development of neuropathic pain in Rodents . Is is all about Pain? . *Pain Practice,* 3**,** 326-342.

Vogt, B. A., Hof, P. R., Friedman, D. P., Sikes, R. W. & Vogt, L. J. 2008. Norepinephrinergic Afferents and Cytology of the Macaque Monkey Midline, Mediodorsal, and Intralaminar Thalamic Nuclei. *Brain Structure & Function,* 212**,** 465-479.

Vogt, B. A., Sikes, R. W. & Vogt, L. J. 1993. Anterior cingulate cortex and the medial pain system. In:Neurobiology of Cingulate Cortex and Limbic Thalalmus, Vogt BA, Gabriel M, eds, Birkhauser Boston,. 313-344.

Voscopoulos, C. & Lema, M. 2010. When does acute pain become chronic? *British Journal of Anaesthesia,* 105**,** i69-i85.

Vranken, J. H. 2009. Mechanisms and treatment of neuropathic pain. *Central Nervous System Agents in Medicinal Chemistry,* 9**,** 71-78.

Wada, Y., Yamashita, T., Imai, K., Miura, R., Takao, K., Nishi, M., Takeshima, H., Asano, T., Morishita, R., Nishizawa, K., Kokubun, S. & Nukada, T. 2000. A region of the sulfonylurea receptor critical for a modulation of ATP-sensitive K⁺ channels by G-protein βγ-subunits. *The EMBO Journal,* 19**,** 4915-4925.

Wahab, S. I. A., Abdul, A. B., Yeel, H. C., Alzubain, A. S., Elhassan, M. M. & Syam, M. M. 2008. Anti-tumor activities of analogues derived from the bioactive compound of Zingiber zerumbet. *International Journal of Cancer Research,* 4**,** 154-159.

Walczak, J. S. & Beaulieu, P. 2006. Comparison of three models of neuropathic pain in mice using a new method to assess cold allodynia: the double plate technique. *Neuroscience Letters*, 399**,** 240-244.

Wall, P. D., Devor, M., Inbal, R., Scadding, J. W., Schonfeld, D., Seltzer, Z. & Tomkiewicz, M. M. 1979. Autotomy following peripheral nerve lesions: experimental anaesthesia dolorosa. *Pain*, 7**,** 103-111.

Wall, P. D. & Gutnick, M. 1974. Ongoing activity in peripheral nerves: The physiology and pharmacology of impulses originating from a neuroma. *Experimental Neurology*, 43**,** 580-593.

Wan, L., Luo, A., Yu, H. & Tian, Y. 2005. Effect of touch-stimulus on the expression of C-fos and TrkA in spinal cord following chronic constriction injury of the sciatic nerve in rats. *Journal of Huazhong University of Science and Technology. Medical sciences*, 25**,** 219-222.

Wang, C. C., Willis, W. D. & Westlund, K. N. 1999. Ascending projections from the area around the spinal cord central canal: a Phaseolus vulgaris leucoagglutinin study in rats. *Journal of Comparative Neurology*, 415**,** 341-367.

Watanabe, K., Konno, S., Sekiguchi, M., Sasaki, N., Honda, T. & Kikuchi, S. 2007. Increase of 200-kDa neurofilament-immunoreactive afferents in the substantia gelatinosa in allodynic rats induced by compression of the dorsal root ganglion. *Spine (Phila Pa 1976)*, 32**,** 1265-1271.

Weerasuriya, A. & Mizisin, A. P. 2011. The blood-nerve barrier: structure and functional significance. *Methods in Molecular Biology*, 686**,** 149-173.

Wells, M. R., Racis, S. P., Jr. & Vaidya, U. 1992. Changes in plasma cytokines associated with peripheral nerve injury. *Journal of Neuroimmunology*, 39**,** 261-268.

Wenhong, D., Jia, Y., Weixing, W., Xiaoyan, C., Chen, C., Sheng, X. & Hao, J. 2012. Zerumbone Attenuates the Severity of Acute Necrotizing Pancreatitis and Pancreatitis-Induced Hepatic Injury. *Mediators of Inflammation*, 2012**,** 12.

White, F. V., Toews, A. D., Goodrum, J. F., Novicki, D. L., Bouldin, T. W. & Morell, P. 1989. Lipid metabolism during early stages of Wallerian degeneration in the rat sciatic nerve. *Journal of Neurochemistry*, 52**,** 1085-1092.

Whitehead, K. J., Smith, C. G., Delaney, S. A., Curnow, S. J., Salmon, M., Hughes, J. P. & Chessell, I. P. 2010. Dynamic regulation of spinal pro-inflammatory cytokine release in the rat in vivo following peripheral nerve injury. *Brain, Behavior, and Immunity*, 24**,** 569-576.

Whiteside, G. T., Adedoyin, A. & Leventhal, L. 2008. Predictive validity of animal pain models? A comparison of the pharmacokinetic -pharmacodynamic relationship for pain drugs in rats and humans. *Neuropharmacology*, 54**,** 767-775.

WHO. 2008. "Traditional Medicine: Definitions". World Health Organization. 2008-12-01. Retrieved 2016-12-20.

Williams, S., Evan, G. I. & Hunt, S. P. 1990. Changing patterns of c-fos induction in spinal neurons following thermal cutaneous stimulation in the rat. *Neuroscience*, 36**,** 73-81.

Willis, W. D. & Coggeshall, R. E. 2012. *Sensory Mechanisms of the Spinal Cord: Volume 1 Primary Afferent Neurons and the Spinal Dorsal Horn*, Springer Science & Business Media.

Wolf, G., Gabay, E., Tal, M., Yirmiya, R. & Shavit, Y. 2006. Genetic impairment of interleukin-1 signaling attenuates neuropathic pain, autotomy, and spontaneous ectopic neuronal activity, following nerve injury in mice. *Pain*, 120**,** 315-324.

Woolf, C. J. & Ma, Q. 2007. Nociceptors—Noxious Stimulus Detectors. *Neuron,* 55**,** 353-364.

Woolf, C. J. & Mannion, R. J. 1999. Neuropathic pain: aetiology, symptoms, mechanisms, and management. *Lancet,* 353**,** 1959-1964.

Woolf, C. J., Shortland, P. & Coggeshall, R. E. 1992. Peripheral nerve injury triggers central sprouting of myelinated afferents. *Nature,* 355**,** 75-78.

Woolf, C. J., Shortland, P., Reynolds, M., Ridings, J., Doubell, T. & Coggeshall, R. E. 1995. Reorganization of central terminals of myelinated primary afferents in the rat dorsal horn following peripheral axotomy. *The Journal of Comparative Neurology,* 360**,** 121-134.

Wright, D. F. B., Winter, H. R. & Duffull, S. B. 2011. Understanding the time course of pharmacological effect: a PKPD approach. *British Journal of Clinical Pharmacology,* 71**,** 815-823.

Wu, Y. E., Li, Y., D., Luo, Y. J., Wang, T. X., Wang, H. J., Chen, S. N., Qu, W. M. & Huang, Z., L. 2015. Gelsemine alleviates both neuropathic pain and sleep disturbance in partial sciatic nerve ligation mice. *Acta Pharmacologica Sinica,* 36**,** 1308-1317.

Wulf-Johansson, H., Hay-Schmidt, A., Poulsen, A. N., Klaerke, D. A., Olesen, J. & Jansen-Olesen, I. 2009. Expression of BKCa channels and the modulatory β-subunits in the rat and porcine trigeminal ganglion. *Brain Research,* 1292**,** 1-13.

Wulff, H., Castle, N. A. & Pardo, L. A. 2009. Voltage-gated Potassium Channels as Therapeutic Drug Targets. *Nature reviews. Drug discovery,* 8**,** 982-1001.

Wuttke, T. V., Seebohm, G., Bail, S., Maljevic, S. & Lerche, H. 2005. The new anticonvulsant retigabine favors voltage-dependent opening of the Kv7.2 (KCNQ2) channel by binding to its activation gate. *Molecular Pharmacology,* 67**,** 1009-1017.

Xu, H., Wu, L. J., Wang, H., Zhang, X., Vadakkan, K. I., Kim, S. S., Steenland, H. W. & Zhuo, M. 2008. Presynaptic and postsynaptic amplifications of neuropathic pain in the anterior cingulate cortex. *Journal of Neuroscience,* 28**,** 7445-7453.

Yamada, K. & Inagaki, N. 2005. Neuroprotection by KATP channels. *Journal of Molecular and Cellular Cardiology,* 38**,** 945-949.

Yang, E. K., Takimoto, K., Hayashi, Y., De Groat, W. C. & Yoshimura, N. 2004. Altered expression of potassium channel subunit mRNA and alpha-dendrotoxin sensitivity of potassium currents in rat dorsal root ganglion neurons after axotomy. *Neuroscience,* 123**,** 867-874.

Yob, N. J., Jofrry, S. M., Affandi, M. M. R. M. M., Teh, L. K., Salleh, M. Z. & Zakaria, Z. A. 2011. Zingiber zerumbet (L.) Smith: A Review of Its Ethnomedicinal, Chemical, and Pharmacological Uses. *Evidence-Based Complementary and Alternative Medicine***,** 12.

Yowtak, J., Lee, K. Y., Kim, H. Y., Wang, J., Kim, H. K., Chung, K. & Chung, J. M. 2011. Reactive oxygen species contribute to neuropathic pain by reducing spinal GABA release. *Pain,* 152**,** 844-852.

Zakaria, Z. A., Mohamad, A. S., Chear, C. T., Wong, Y. Y., Israf, D. A. & Sulaiman, M. R. 2010. Antiinflammatory and antinociceptive activities of Zingiber zerumbet methanol extract in experimental model systems. *Medical Principles and Practice,* 19**,** 287-294.

Zamponi, G. W. & Snutch, T. P. 2002. Modulating modulation: crosstalk between regulatory pathways of presynaptic calcium channels. *Molecular Interventions,* 2**,** 476-478.

Zhang, W., Xiao-Feng, S., Jin-Hua, B., Xiso-Jie, L., Liu-Ping, W., Zheng-Liang, M. & Xiao-Ping, G. 2013. Activation of mTOR in the spinal cord is required for pain hypersensitivity induced by chronic constriction injury in mice. *Pharmacology, Biochemistry and Behavior,* 111**,** 64-70.

Zheng, Q., Fang, D., Liu, M., Cai, J., Wan, Y., Han, J. S. & Xing, G. G. 2013. Suppression of KCNQ/M (Kv7) potassium channels in dorsal root ganglion neurons contributes to the development of bone cancer pain in a rat model. *Pain,* 154**,** 434-448.

Zick, S. M., Djuric, Z., Ruffin, M. T., Litzinger, A. J., Normolle, D. P., Feng, M. R. & Brenner, D. E. 2008. Pharmacokinetics of 6-, 8-, 10-Gingerols and 6-Shogaol and Conjugate Metabolites in Healthy Human Subjects. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology,* 17**,** 1930-1936.

Zimmerman, M. E., Pan, J. W., Hetherington, H. P., Lipton, M. L., Baigi, K. & Lipton, R. B. 2009. Hippocampal correlates of pain in healthy elderly adults: A pilot study. *Neurology,* 73**,** 1567-1570.

Zimmermann, M. 2001. Pathobiology of neuropathic pain. *European Journal of Pharmacology,* 429**,** 23-37.

Zoga, V., Kawano, T., Liang, M. Y., Bienengraeber, M., Weihrauch, D., Mccallum, B., Gemes, G., Hogan, Q. & Sarantopoulos, C. 2010. KATP channel subunits in rat dorsal root ganglia: alterations by painful axotomy. *Molecular Pain,* 6**,** 6.

Zulazmi, N. A., Gopalsamy, B., Farouk, A. a. O., Sulaiman, M. R., Bharatham, B. H. & Perimal, E. K. 2015. Antiallodynic and antihyperalgesic effects of zerumbone on a mouse model of chronic constriction injury-induced neuropathic pain. *Fitoterapia,* 105**,** 215–221.

Zushida, K., Onodera, K. & Kamei, J. 2002. Effect of diabetes on pinacidil-induced antinociception in mice. *European Journal of Pharmacology,* 453**,** 209-215.

Ÿceyler, N., Tscharke, A. & Sommer, C. 2007. Early cytokine expression in mouse sciatic nerve afterchronic constriction nerve injury depends on calpain. *Brain, Behavior, and Immunity,* 21**,** 553-560.